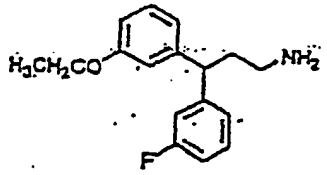
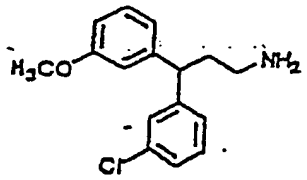
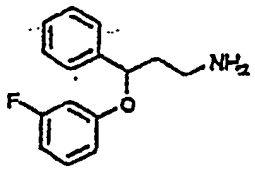


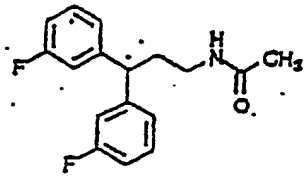
Compound 135



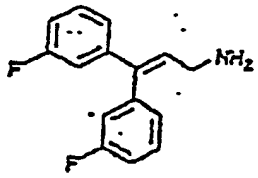
Compound 136



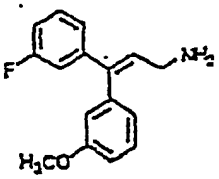
Compound 137



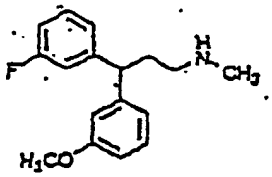
Compound 138



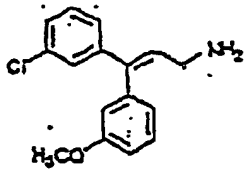
Compound 139



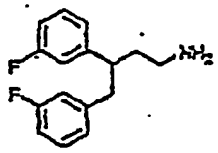
Compound 141



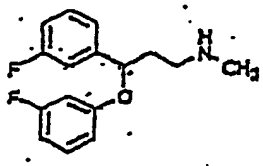
Compound 142



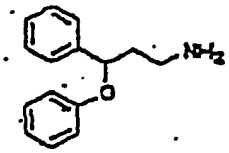
Compound 143



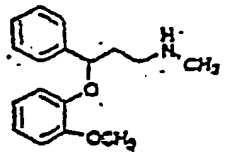
Compound 144



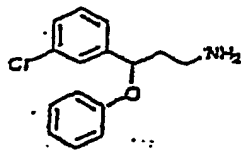
Compound 145



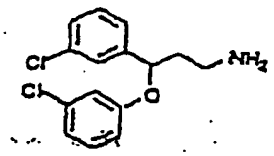
Compound 146



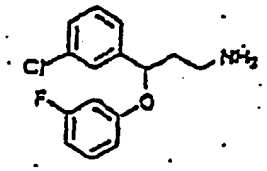
Compound 147



Compound 148



Compound 149



Compound 150

, and pharmaceutically acceptable salts and complexes thereof for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

2. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

3. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-97, 100- 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150, and pharmaceutically acceptable salts and complexes thereof.

4. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

5. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150, and pharmaceutically acceptable salts and complexes thereof.

6. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 82, 83, 89-90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

7. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

8. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 118-122, 137, 145, 148-150, and pharmaceutically acceptable salts and complexes thereof.

9. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 118-122, 148-150, and pharmaceutically acceptable salts and complexes thereof.

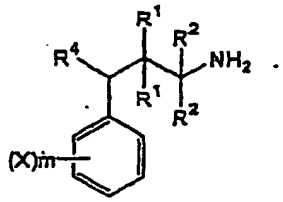
10. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 63 and 64 and pharmaceutically acceptable salts and complexes thereof.

11. The use according to claim 1, wherein the compound is selected from compound 119, and pharmaceutically acceptable salts and complexes thereof.

12. The use according to claim 1, wherein the compound is selected from compound 144, and pharmaceutically acceptable salts and complexes thereof.

13. The use of compound 60, and pharmaceutically acceptable salts and complexes thereof for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

14. Use of a compound having the formula:

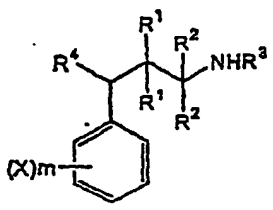


wherein:

X is independently selected from the group consisting of -Br, -Cl, -F, -I,-CF_3, alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH,- OCF_3-O-alkyl, or -O-acyl; and
m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not:
3-(p-isopropoxyphenoxy)-3-phenylpropylamine
3-(2'-methyl-4',5'-dichlorophenoxy)-3-phenylpropylamine
3-(p-t-butylphenoxy)-3-phenylpropylamine
3-(2',4'-dichlorophenoxy)-3-phenyl-2-methyl propylamine
3-(o-ethylphenoxy)-3-phenylpropylamine
3-(o-methoxyphenoxy)-3-phenylpropylamine
3-phenoxy-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

15. Use of a compound having the formula

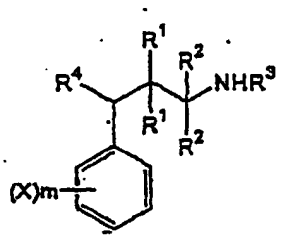


wherein:

X is independently selected from the group consisting of-F, -Cl, -Br, -I, -CF_3 alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not
N-methyl 3-(o-chloro-p-tolyloxy)-3-phenyl-1-methylpropylamine
N-methyl 3-(p-tolyloxy)-3-phenylpropylamine
N-methyl 3-(o-chloro-p-isopropylphenoxy)-3-phenyl-2-methylpropylamine
N-methyl 3-(p-iodophenoxy)-3-phenyl-propylamine
N-methyl 3-(3-n propylphenoxy)-3-phenyl-propylamine
N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-phenoxy-3-phenyl-2-methylpropylamine
N-methyl 3-phenoxy-3-phenyl-1-methylpropylamine
N-methyl 3-phenoxy-3-phenylpropylamine
N-methyl 3-(o-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o,p-difluorophenoxy)-3-phenylpropylamine
N-ethyl-3-(o-iodophenoxy)-3-phenylpropylamine
N-methyl-3-(o-chlorophenoxy)-3-phenylpropylamine
N-methyl-3-(o-bromophenoxy)-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

16. Use of a compound having the formula:



wherein:

(X)m is selected from the group consisting of meta-fluoro, meta-chloro, Ortho-O-C_1-C_4 alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O-C_1-C_4 alkyl, meta-methyl, ortho-OH, and meta-OH;
R_1 is H;
R_2 is H;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and pharmaceutically acceptable salts and complexes thereof, for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

17. The use of any one of claims 1 to 16, wherein the neurological disease or disorder comprises stroke, head trauma, spinal cord injury, spinal cord ischemia, ischemia- or hypoxia-induced nerve cell damage, epilepsy, pain, anxiety, neuropsychiatric or cognitive deficits due to ischemia or hypoxia such as those that frequently occur as a consequence of cardiac surgery under cardiopulmonary bypass, Alzheimer's disease, Huntington's disease, Parkinson's disease, or amyotyrophic lateral sclerosis.

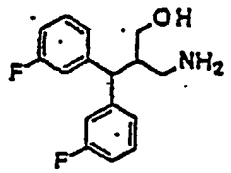
18. The use of claim 17, wherein said stroke is global ischemic.

19. The use of claim 17, wherein said stroke is focal ischemic.

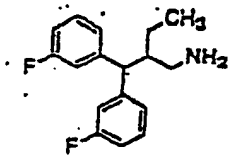
20. The use of claim 17, wherein said stroke is hemorrhagic.

21. The use of claim 17, wherein the neurological disease or disorder comprises Parkinson's disease.

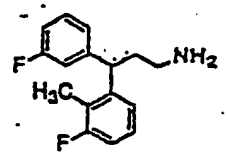
22. A compound selected from the group consisting of



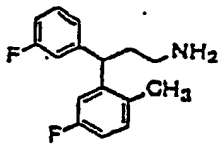
Compound 54



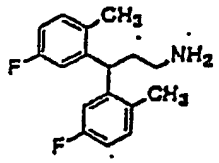
Compound 55



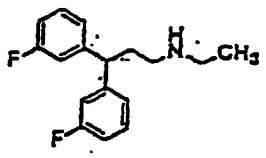
Compound 56



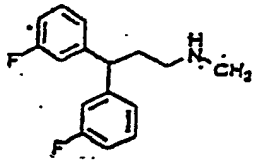
Compound 57



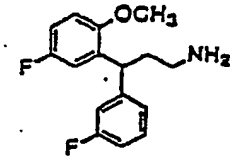
Compound 58



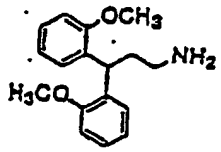
Compound 59



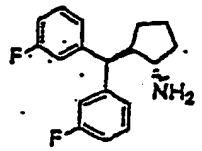
Compound 60



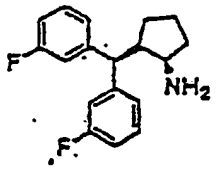
Compound 61



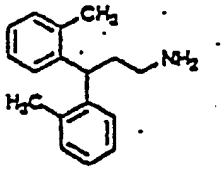
Compound 62



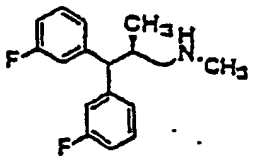
Compound 63



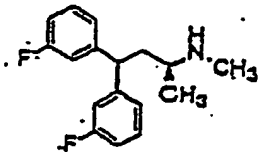
Compound 64



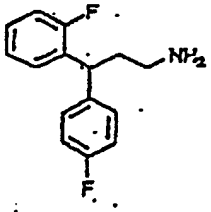
Compound 65



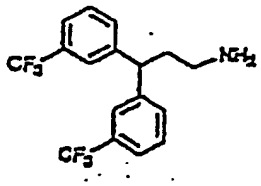
Compound 66



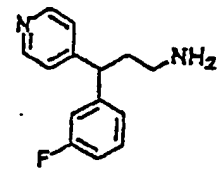
Compound 69



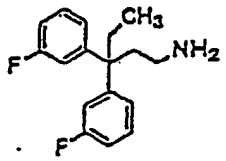
Compound 76



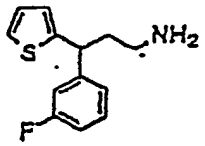
Compound 78



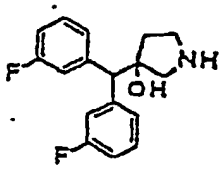
Compound 79



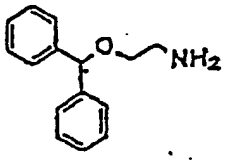
Compound 82



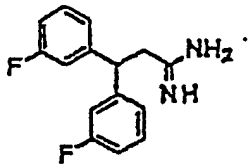
Compound 83



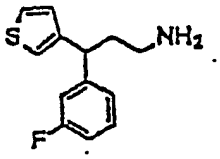
Compound 84



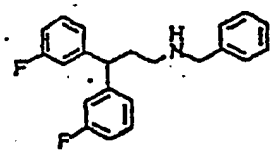
Compound 88



Compound 89



Compound 90



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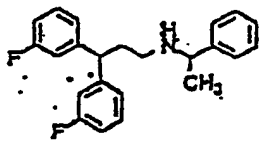
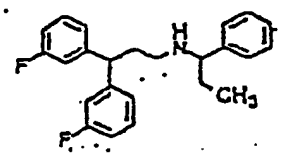
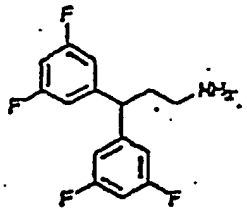


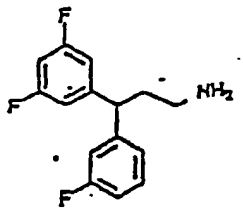
Compound 93



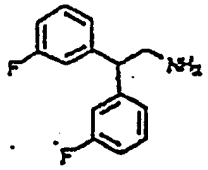
Compound 94



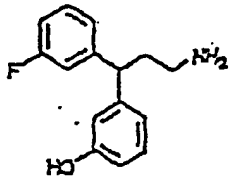
Compound 95



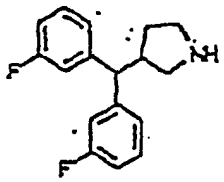
Compound 96



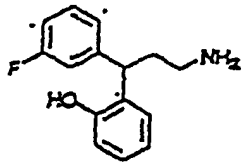
Compound 98



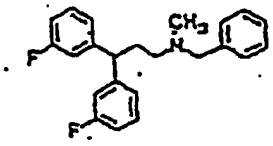
Compound 101



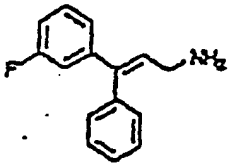
Compound 102

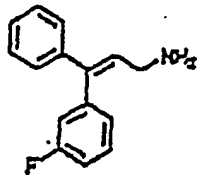


Compound 103

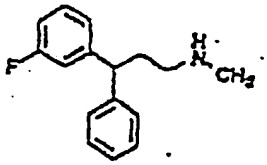


Compound 105

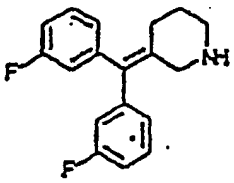




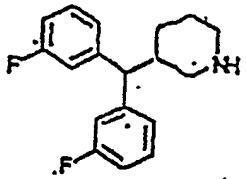
Compound 107
(mixture of 2
compounds)



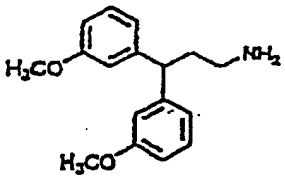
Compound 108



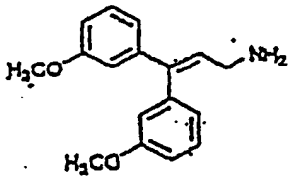
Compound 109



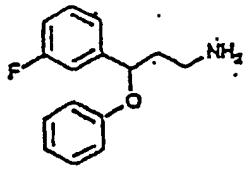
Compound 111



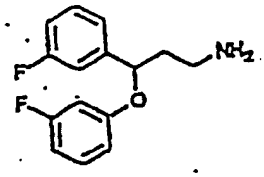
Compound 115



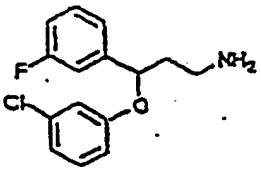
Compound 116



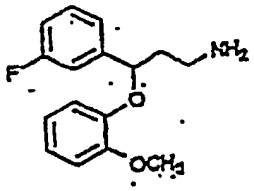
Compound 118



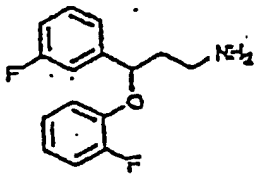
Compound 119



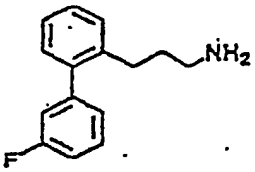
Compound 120



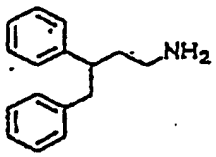
Compound 121



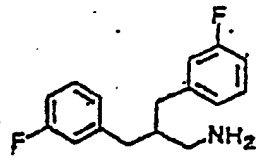
Compound 122



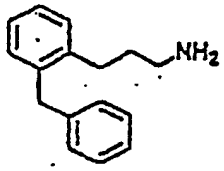
Compound 124



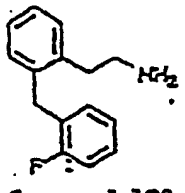
Compound 125



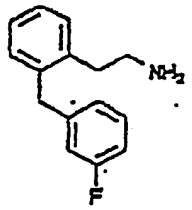
Compound 126



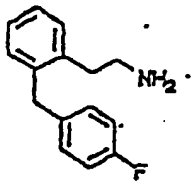
Compound 127



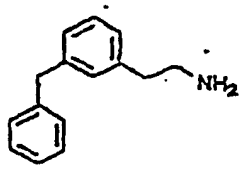
Compound 129



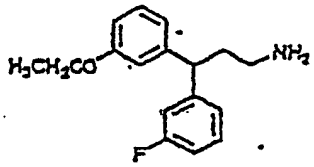
Compound 130



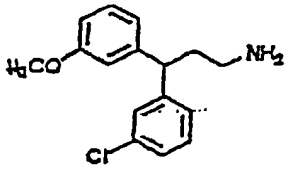
Compound 131



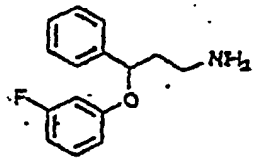
Compound 134



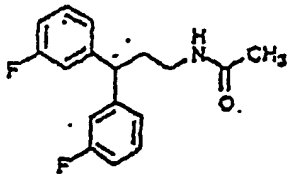
Compound 135



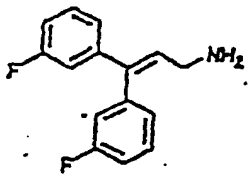
Compound 136



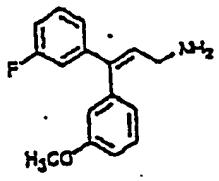
Compound 137



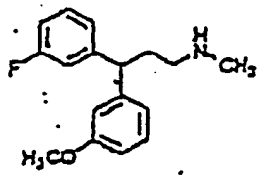
Compound 138



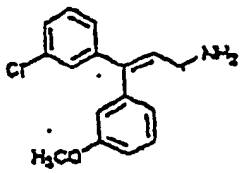
Compound 139



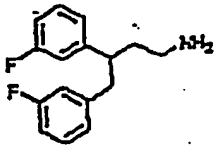
Compound 141



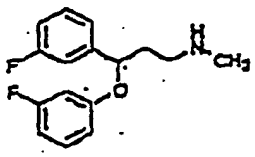
Compound 142



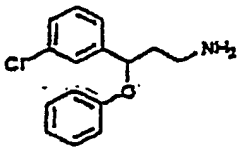
Compound 143



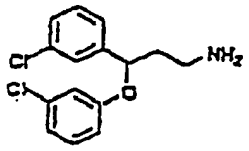
Compound 144



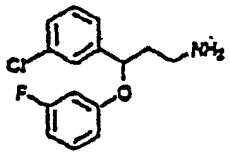
Compound 145



Compound 148



Compound 149



Compound 150

and pharmaceutically acceptable salts thereof.

23. The compound according to claim 22, selected from the group consisting of compounds 54-66, 69, 76, 82, 83,

88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131, 135-139, 142, 144, 145, 148-150, or pharmaceutically acceptable salts thereof.

24. The compound according to claim 22, selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111,118-120, 122, 126, 135-138, 142,144,145,148-150, or pharmaceutically acceptable salts thereof.

25. The compound according to claim 22, selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, or pharmaceutically acceptable salts thereof.

26. The compound according to claim 22, selected from the group consisting of compounds 118-122, 137, 145, 148-150, or pharmaceutically acceptable salts thereof.

27. The compound according to claim 22, selected from the group consisting of compounds 118-122,148-150, or pharmaceutically acceptable salts thereof.

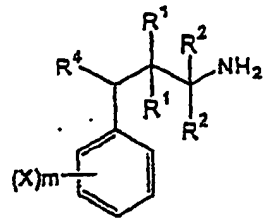
28. The compound according to claim 22, selected from the group consisting of compounds 63 and 64, or pharmaceutically acceptable salts thereof.

29. The compound according to claim 22, which is compound 119, or pharmaceutically acceptable salts thereof.

30. The compound according to claim 22, which is compound 144, or pharmaceutically acceptable salts thereof.

31. Compound 60, or pharmaceutically acceptable salts thereof.

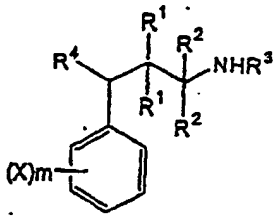
32. A compound of the formula:



wherein:

X is independently selected from the group consisting of -Br, -Cl, -F, -I,-CF_3, alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH,- OCF_3 -O-alkyl, or -O-acyl; and
m is independently an integer from 1 to 5; and pharmaceutically acceptable salts and complexes thereof:

33. A compound of the formula:

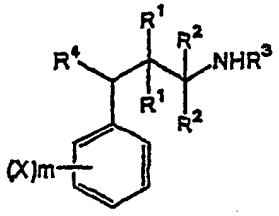


wherein:

X is independently selected from the group consisting of -F, -Cl, -Br, -I, -CF_3 alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of-H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of-H, C_1-C_4 alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl;

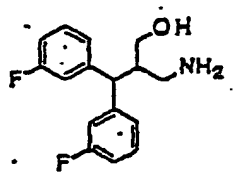
and m is independently an integer from 1 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not N-methyl 3-(m-trifluoromethylphenoxy)-3-(4-fluorophenyl)propylamine.

34. A compound of the formula:

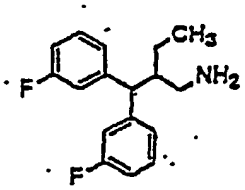


(X)m is selected from the group consisting of meta-fluoro, meta-chloro, ortho-O-C_1-C_4 alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O- C_1-C_4 alkyl, meta-methyl, ortho-OH, and meta-OH;
R_1 is H;
R_2 is H;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and pharmaceutically acceptable salts and complexes thereof.

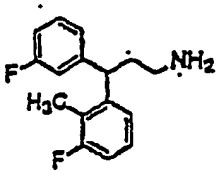
35. A pharmaceutical composition comprising a compound which is selected from the group consisting of



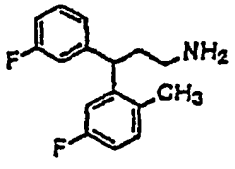
Compound 54



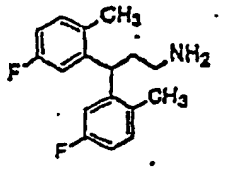
Compound 55



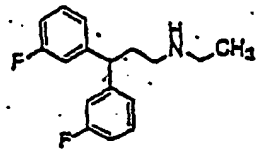
Compound 56



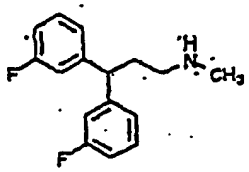
Compound 57



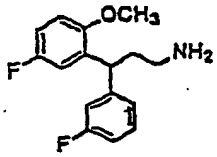
Compound 58



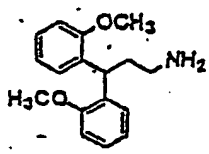
Compound 59



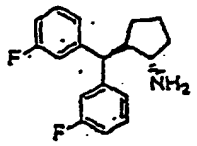
Compound 60



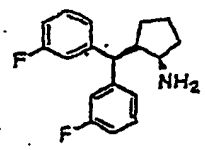
Compound 61



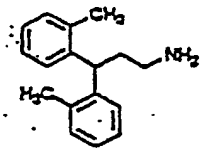
Compound 62



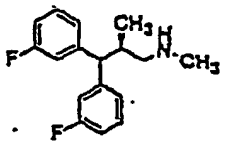
Compound 63



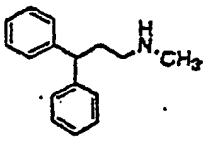
Compound 64



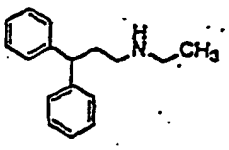
Compound 65



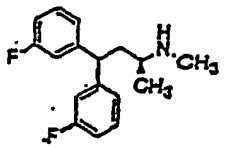
Compound 66



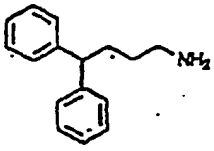
Compound 67



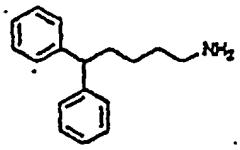
Compound 68



Compound 69



Compound 70



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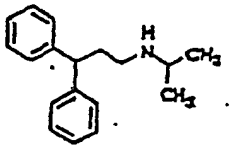
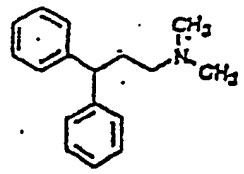
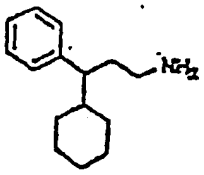


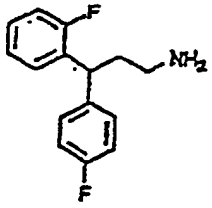
Compound 72



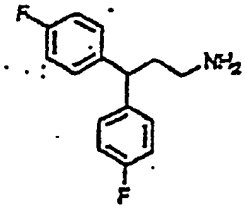
Compound 73



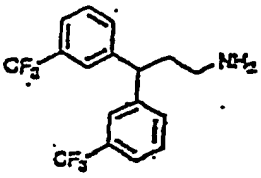
Compound 75



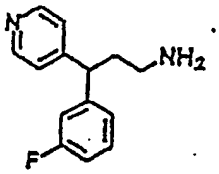
Compound 76



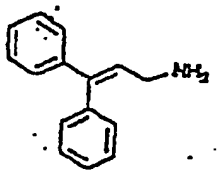
Compound 77



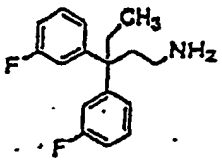
Compound 78



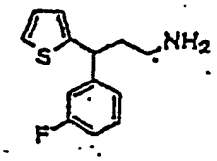
Compound 79



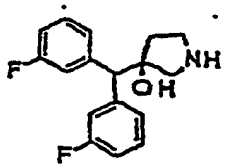
Compound 81



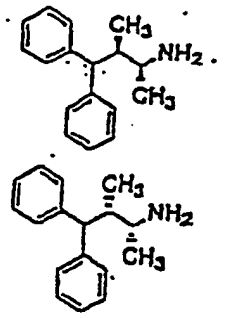
Compound 82



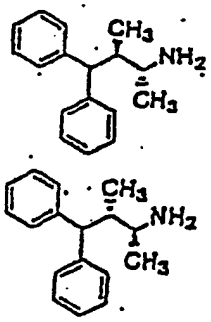
Compound 83



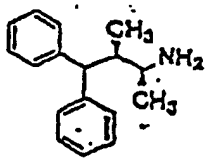
Compound 84



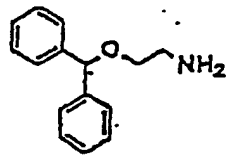
Compound 85
(mixture of 2
compounds)



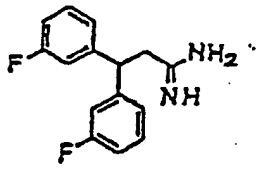
Compound 86
(mixture of 2
compounds)



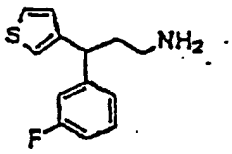
Compound 87



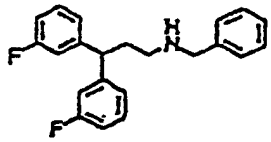
Compound 88



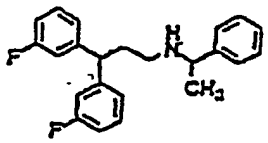
Compound 89



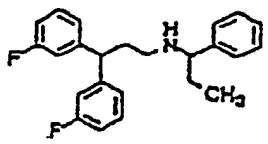
Compound 90



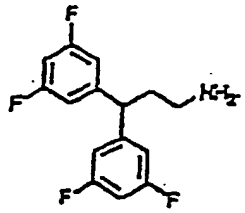
Compound 92



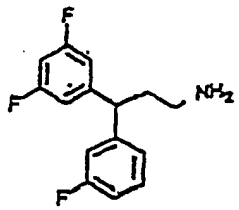
Compound 93



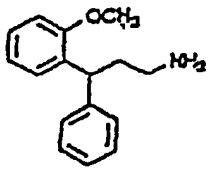
Compound 94



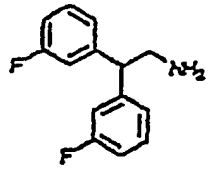
Compound 95



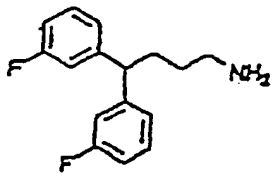
Compound 96



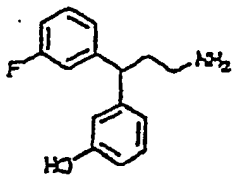
Compound 97



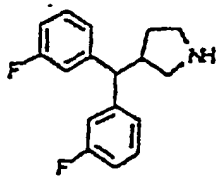
Compound 98



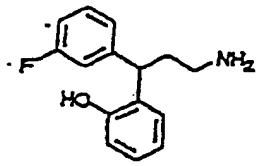
Compound 100



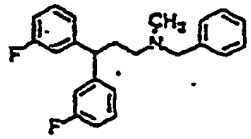
Compound 101



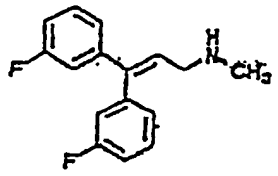
Compound 102



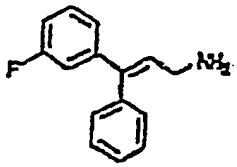
Compound 103

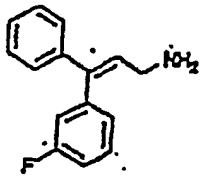


Compound 105

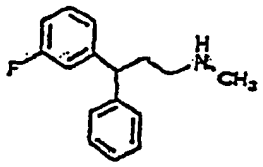


Compound 106

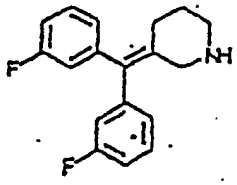




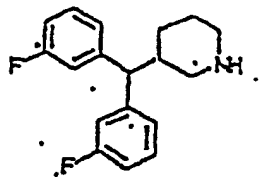
Compound 107
(mixture of 2
compounds)



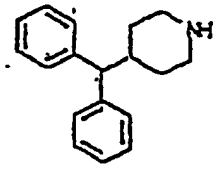
Compound 108



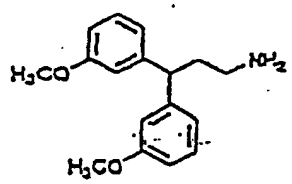
Compound 109



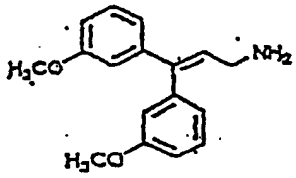
Compound 111



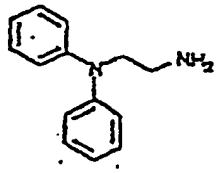
Compound 114



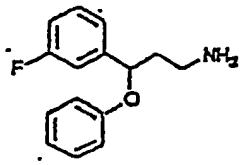
Compound 115



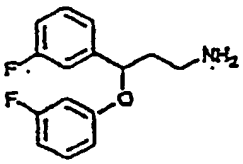
Compound 116



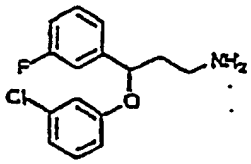
Compound 117



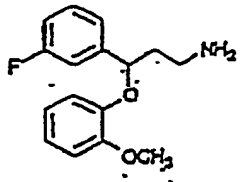
Compound 118



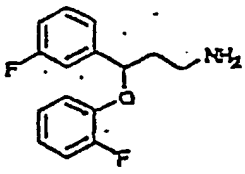
Compound 119



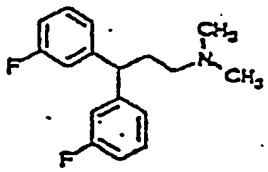
Compound 120



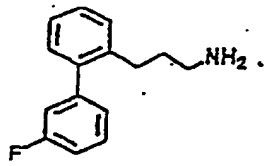
Compound 121



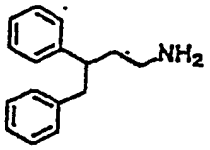
Compound 122



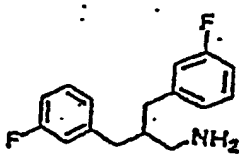
Compound 123



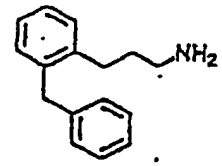
Compound 124



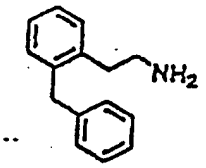
Compound 125



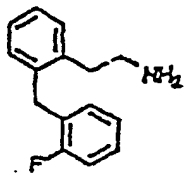
Compound 126



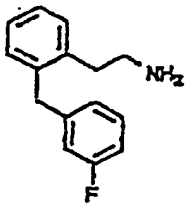
Compound 127



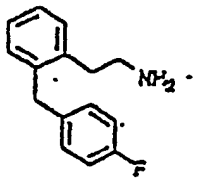
Compound 128



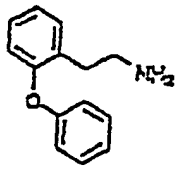
Compound 129



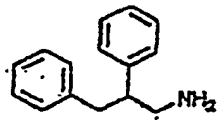
Compound 130



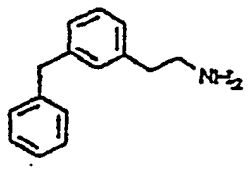
Compound 131



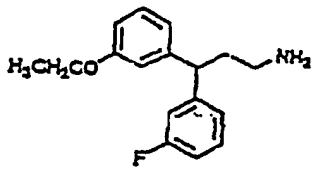
Compound 132



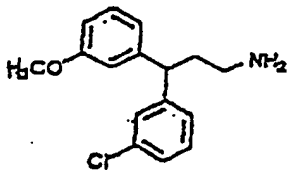
Compound 133



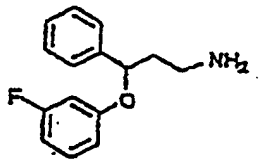
Compound 134



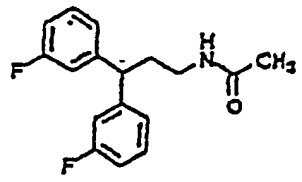
Compound 135



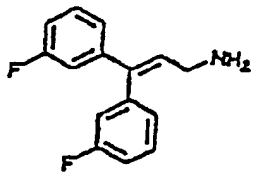
Compound 136



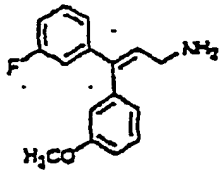
Compound 137



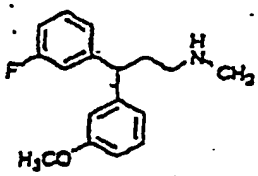
Compound 138



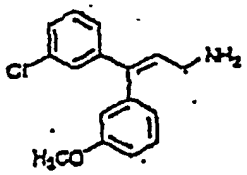
Compound 139



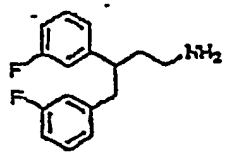
Compound 141



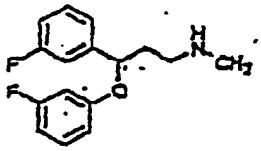
Compound 142



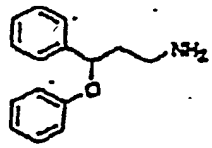
Compound 143



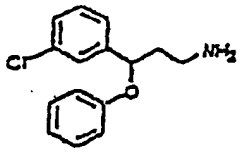
Compound 144



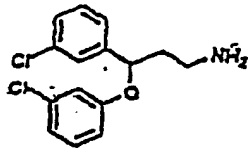
Compound 145



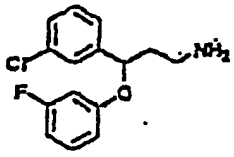
Compound 146



Compound 148



Compound 149



Compound 150

and pharmaceutically acceptable salts thereof in a pharmaceutically acceptable carrier.

36. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

37. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

38. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

39. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135- 138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

40. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

41. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

42. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 118-122, 137, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

43. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 118-122, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

44. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 63 and 64, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

45. The pharmaceutical composition according to claim 35, comprising a compound selected from compound 119, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

46. The pharmaceutical composition according to claim 35, comprising a compound selected from compound 144, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

47. A pharmaceutical composition comprising a compound selected from compound 60, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

48. A pharmaceutical composition comprising a compound of claim 32, in a phamiaceutically acceptable carrier.

49. A pharmaceutical composition comprising a compound of claim 33, in a pharmaceutically acceptable carrier.

50. A pharmaceutical composition comprising a compound of claim 34, in a pharmaceutically acceptable carrier.

51. The pharmaceutical composition of any one of claims 35-50 adapted for the treatment of a neurological disease or disorder.

52. The pharmaceutical composition of claim 51, wherein said neurological disease or disorder is selected from the group consisting of stroke, head trauma, spinal cord injury, epilepsy, anxiety, Alzheimer's disease, Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis.

53. The pharmaceutical composition of claim 51, wherein said pharmaceutical composition has neuroprotectant activity.

54. The pharmaceutical composition of claim 52, wherein said stroke is global ischemic.

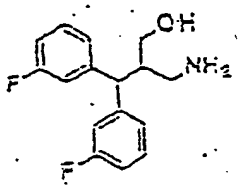
55. The pharmaceutical composition of claim 52, wherein said stroke is focal ischemic.

56. The pharmaceutical composition of claim 52, wherein said stroke is hemorrhagic.

57. The pharmaceutical composition of claim 52, wherein said neurological disease or disorder is Parkinson's disease.

Patentansprüche

1. Verwendung einer Verbindung, die'aus



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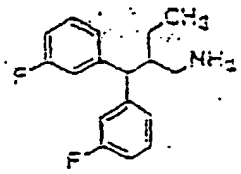

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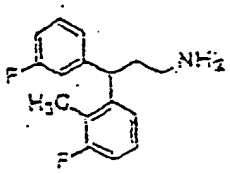

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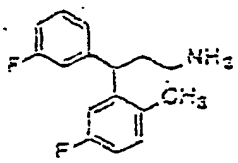

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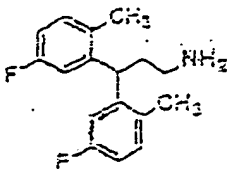

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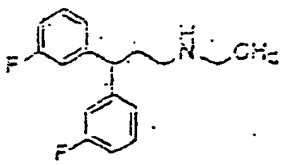

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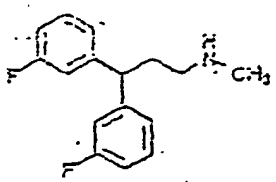

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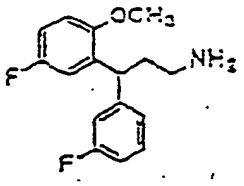

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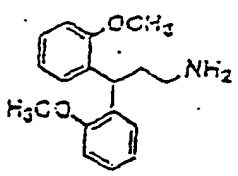

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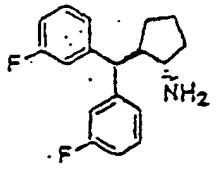

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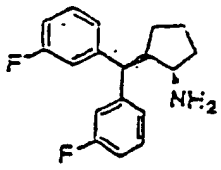

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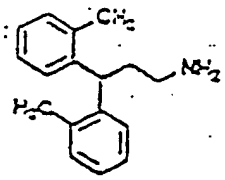

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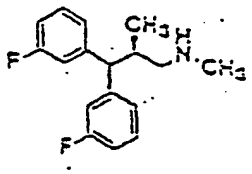

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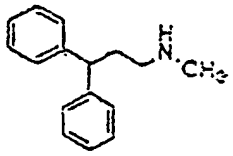

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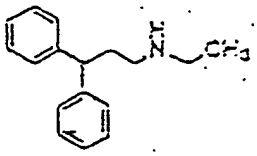

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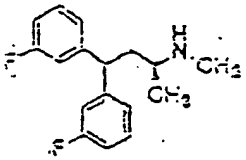

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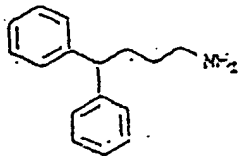

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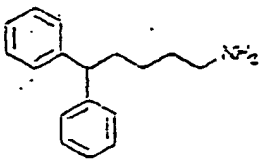

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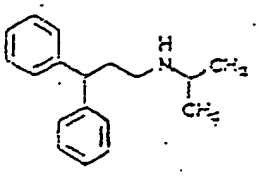

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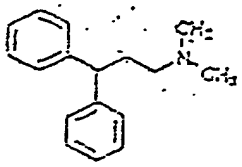

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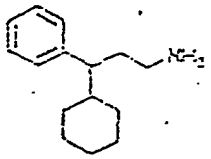

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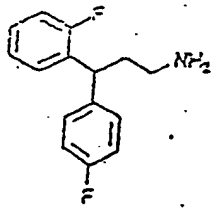

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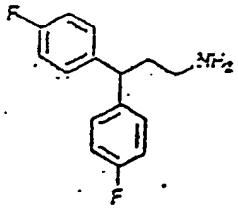

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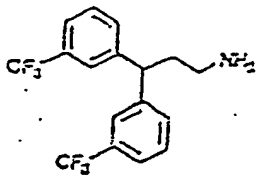

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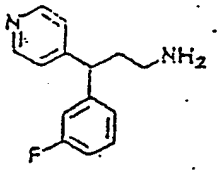

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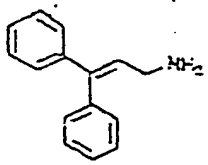

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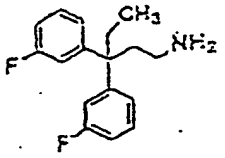

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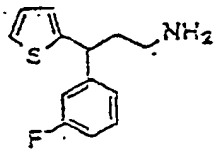

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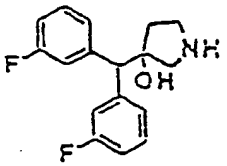

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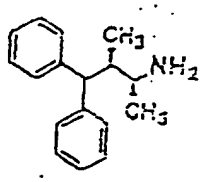

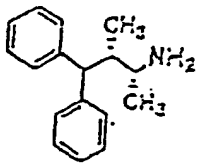

Verbindung 85
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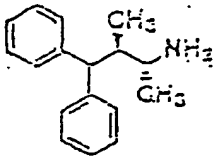

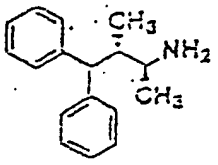

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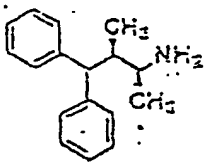

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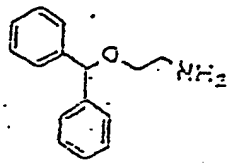

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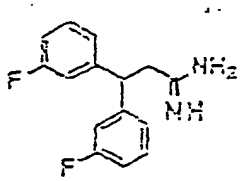

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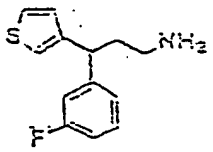

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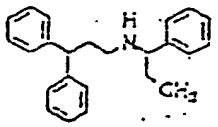

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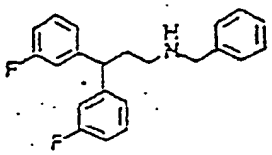

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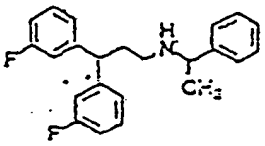

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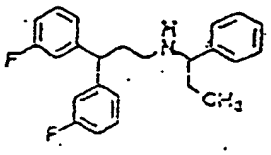

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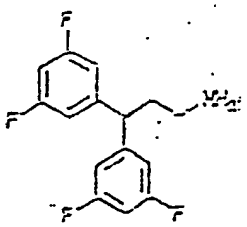

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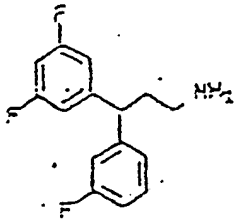

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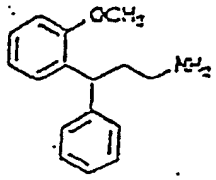

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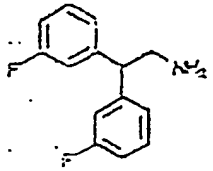

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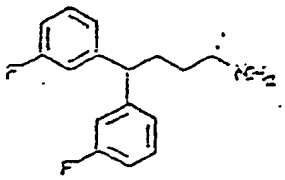

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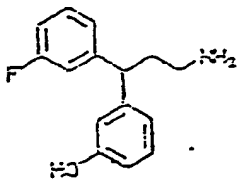

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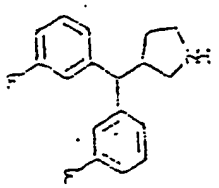
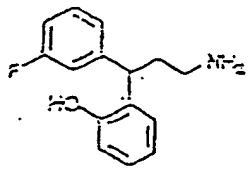


Verbindung 102



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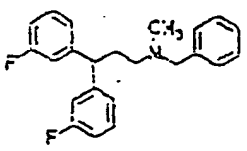

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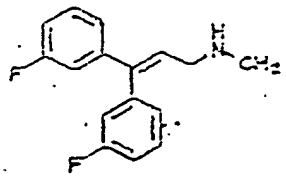

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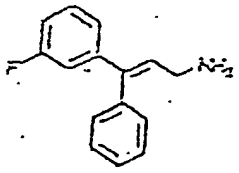
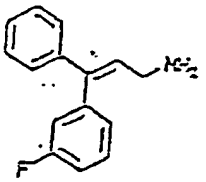
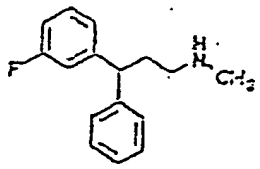
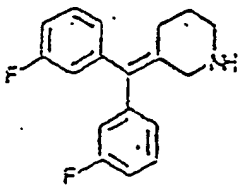




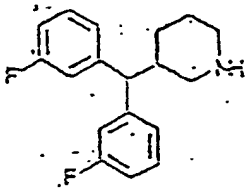
Verbindung 107
(Gemisch aus 2
Verbindungen)



Verbindung 108



Verbindung 109



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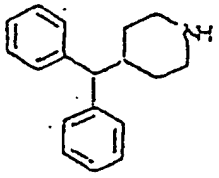

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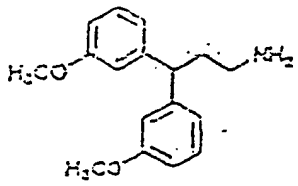

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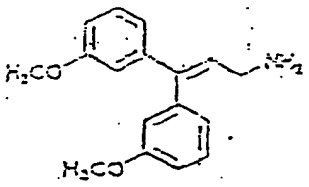

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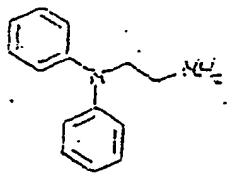
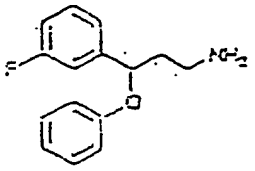
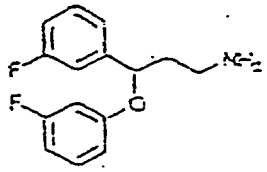


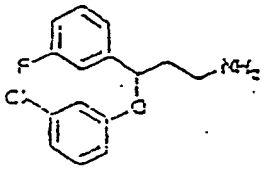
Verbindung 117



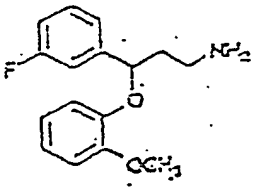
Verbindung 118



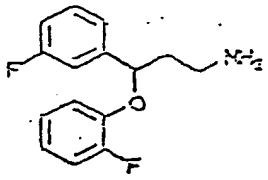
Verbindung 119



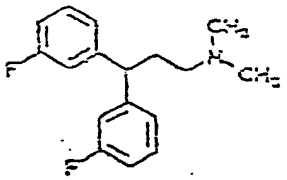
Verbindung 120



Verbindung 121



Verbindung 122



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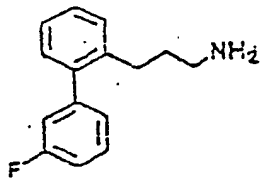
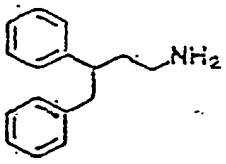


Verbindung 124



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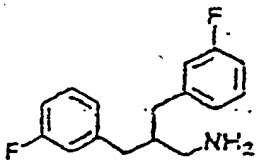
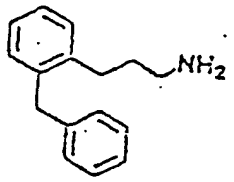


Verbindung 126



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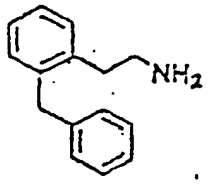
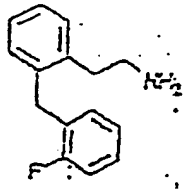
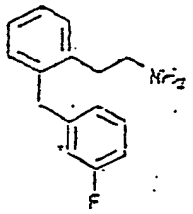


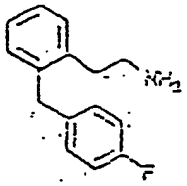
Verbindung 128



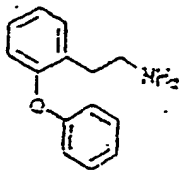
Verbindung 129



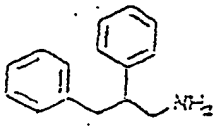
Verbindung 130



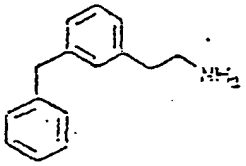
Verbindung 131



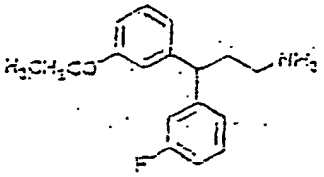
Verbindung 132



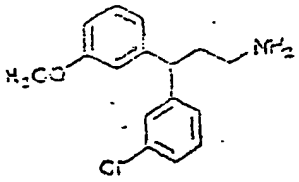
Verbindung 133



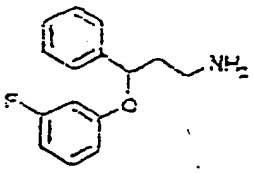
Verbindung 134



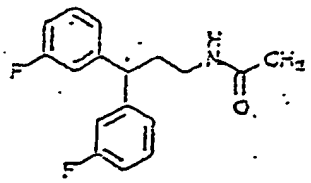
Verbindung 135



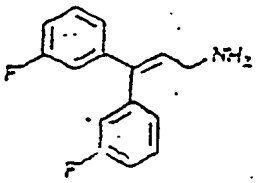
Verbindung 136



Verbindung 137



Verbindung 138



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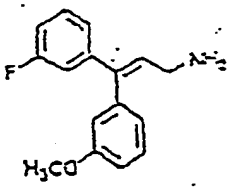
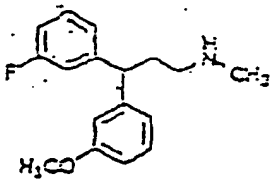
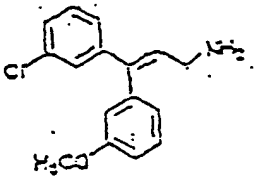


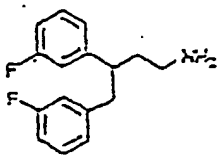
Verbindung 141



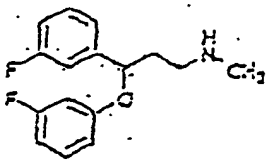
Verbindung 142



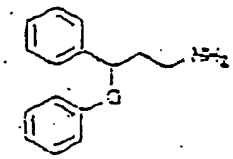
Verbindung 143



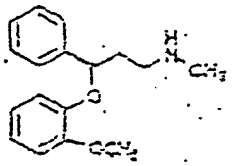
Verbindung 144



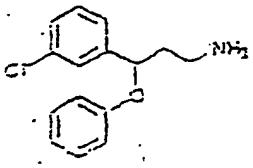
Verbindung 145



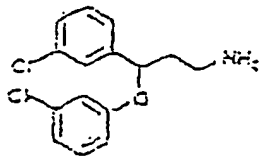
Verbindung 146



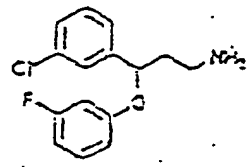
Verbindung 147



Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist, zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

2. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

3. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

4. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

5. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

6. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

7. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

8. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 118-122, 137, 145, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

9. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 118-122, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

10. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 63 und 64 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

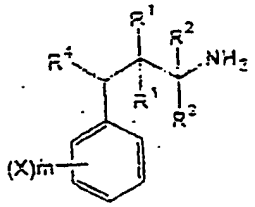
11. Verwendung gemäß Anspruch 1, wobei die Verbindung aus der Verbindung 119 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

12. Verwendung gemäß Anspruch 1, wobei die Verbindung aus der Verbindung 144 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

13. Verwendung von Verbindung 60 und pharmazeutisch verträglichen Salzen und Komplexen davon zur Herstellung

eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

14. Verwendung einer Verbindung der Formel:



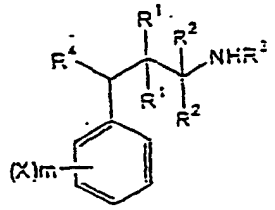
wobei:

X unabhängig aus -Br, -Cl, -F, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 0 bis 5 ist; und pharmazeutisch verträglicher Salze und Komplexe davon mit der Maßgabe, dass die Verbindung nicht:

3-(p-Isopropoxyphenoxy)-3-phenylpropylamin
3-(2'-Methyl-4',5'-dichlorphenoxy)-3-phenylpropylamin
3-(p-t-Butylphenoxy)-3-phenylpropylamin
3-(2',4'-Dichlorphenoxy)-3-phenyl-2-methylpropylamin
3-(o-Ethylphenoxy)-3-phenylpropylamin
3-(o-Methoxyphenoxy)-3-phenylpropylamin
3-Phenoxy-3-phenylpropylamin ist,

zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

15. Verwendung einer Verbindung der Formel:



wobei:

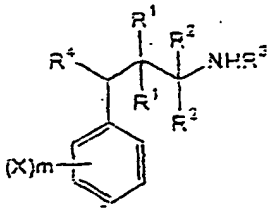
X unabhängig aus -F, -Cl, -Br, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem C_{1-4}-Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl

substituiert ist; und
m unabhängig eine ganze Zahl von 0 bis 5 ist; und pharmazeutisch verträglicher Salze und Komplexe davon, mit der Maßgabe, dass die Verbindung nicht:

N-Methyl-3-(o-chlor-p-tolyloxy)-3-phenyl-1-methylpropylamin
N-Methyl-3-(p-tolyloxy)-3-phenylpropylamin
N-Methyl-3-(o-chlor-p-isopropylphenoxy)-3-phenyl-2-methylpropylamin
N-Methyl-3-(p-iodphenoxy)-3-phenylpropylamin
N-Methyl-3-(3-n-propylphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-trifluormethylphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-tolyloxy)-3-phenylpropylamin
N-Methyl-3-(p-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-phenoxy-3-phenyl-2-methylpropylamin
N-Methyl-3-phenoxy-3-phenyl-1-methylpropylamin
N-Methyl-3-phenoxy-3-phenylpropylamin
N-Methyl-3-(o-trifluormethylphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o,p-difluorphenoxy)-3-phenylpropylamin
N-Ethyl-3-(o-iodphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-bromphenoxy)-3-phenylpropylamin ist,

zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

16. Verwendung einer Verbindung der Formel:



wobei:

(X)m aus einem meta-Fluor-, meta-Chloratom, ortho-O-C_{1-4}-Alkylrest, einer ortho-Methylgruppe, einem ortho-Fluor-, ortho-Chloratom, meta-O-C_{1-4}Alkylrest, einer meta-Methylgruppe, ortho-OH und meta-OH ausgewählt ist;
R_1 H ist;
R_2 H ist;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, -CF_3, Alkyl,-OH, -OCF_3, -O-Alkyl oder -O-Acyl substituiert ist; und
pharmazeutisch verträglicher Salze und Komplexe davon zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

17. Verwendung gemäß einem der Ansprüche 1 bis 16, wobei die neurologische Krankheit oder Störung Schlaganfall, Schädeltrauma, Rückenmarksverletzung, Rückenmarksischämie, eine durch Ischämie oder Hypoxie bedingte Schädigung von Nervenzellen, Epilepsie, Schmerz, Ängstlichkeit, von Ischämie oder Hypoxie ausgelöste neuro-

psychiatrische oder kognitive Defizite, wie diejenigen, die häufig als eine Konsequenz einer Herzchirurgie mit einem kardiopulmonalen Bypass auftreten, Alzheimer-Krankheit, Chorea Huntington, Parkinson-Krankheit oder amyotrophische Lateralsklerose umfasst.

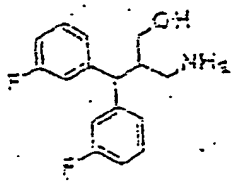
18. Verwendung gemäß Anspruch 17, wobei der Schlaganfall totalischämisch auftritt.

19. Verwendung gemäß Anspruch 17, wobei der Schlaganfall als fokale Ischämie auftritt.

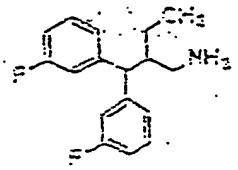
20. Verwendung gemäß Anspruch 17, wobei der Schlaganfall in hemorrhagischer Form auftritt.

21. Verwendung gemäß Anspruch 17, wobei die neurologische Krankheit oder Störung Parkinson-Krankheit umfasst.

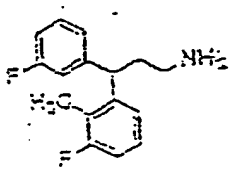
22. Verbindung, ausgewählt aus



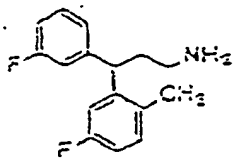
Verbindung 54



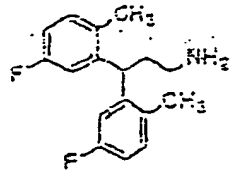
Verbindung 55



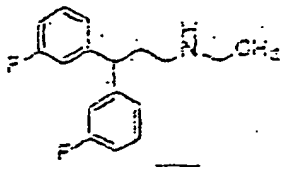
Verbindung 56



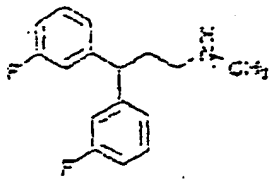
Verbindung 57



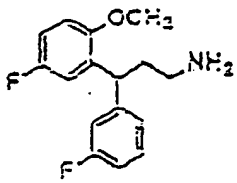
Verbindung 58



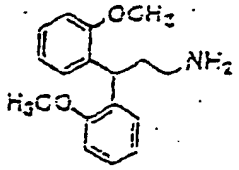
Verbindung 59



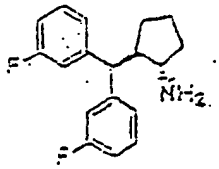
Verbindung 60



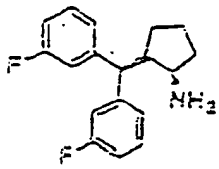
Verbindung 61



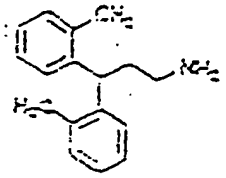
Verbindung 62



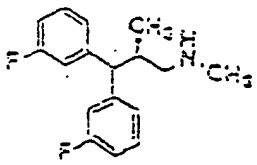
Verbindung 63



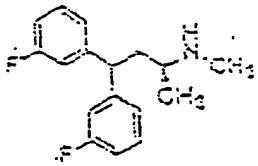
Verbindung 64



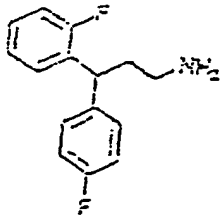
Verbindung 65



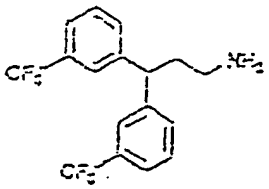
Verbindung 66



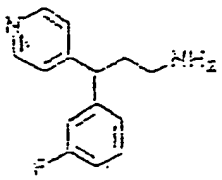
Verbindung 69



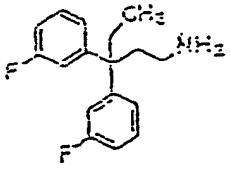
Verbindung 76



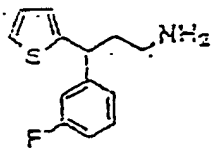
Verbindung 78



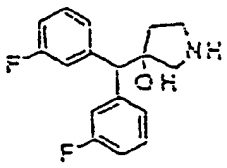
Verbindung 79



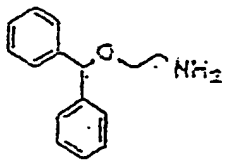
Verbindung 82



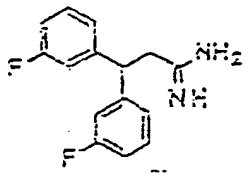
Verbindung 83



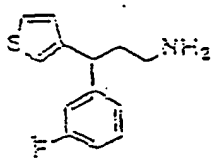
Verbindung 84



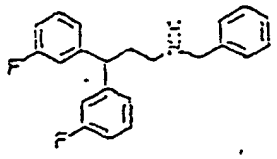
Verbindung 88



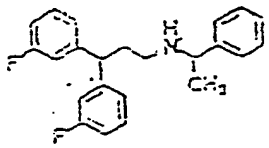
Verbindung 89



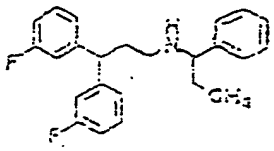
Verbindung 90



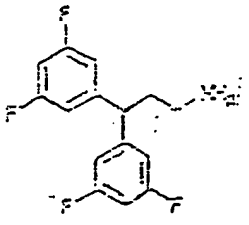
Verbindung 92



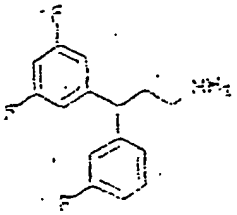
Verbindung 93



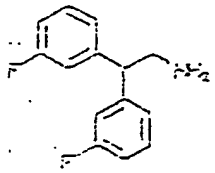
Verbindung 94



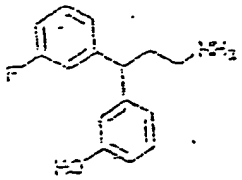
Verbindung 95



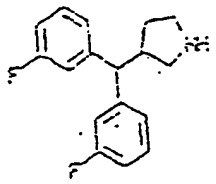
Verbindung 96



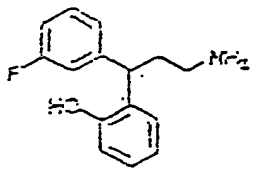
Verbindung 98



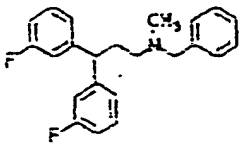
Verbindung 101



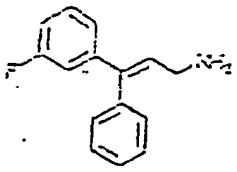
Verbindung 102

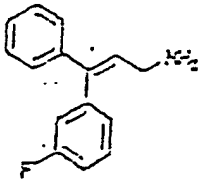


Verbindung 103

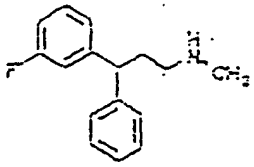


Verbindung 105

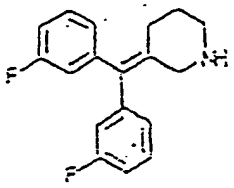




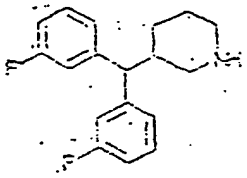
Verbindung 107
(Gemisch aus 2
Verbindungen)



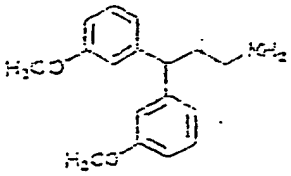
Verbindung 108



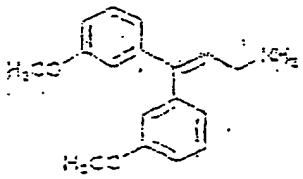
Verbindung 109



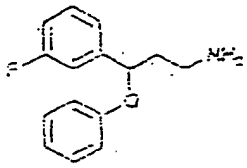
Verbindung 111



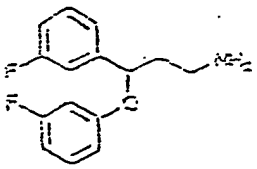
Verbindung 115



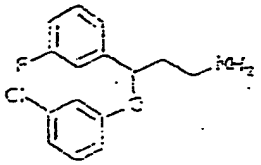
Verbindung 116



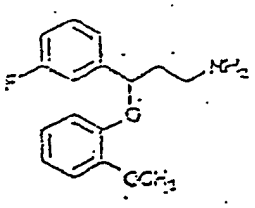
Verbindung 118



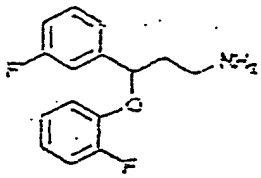
Verbindung 119



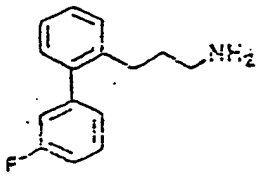
Verbindung 120



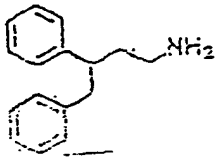
Verbindung 121



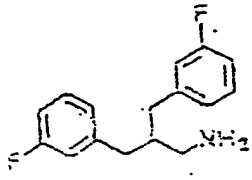
Verbindung 122



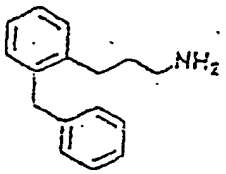
Verbindung 124



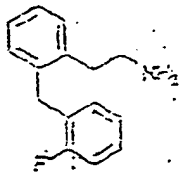
Verbindung 125



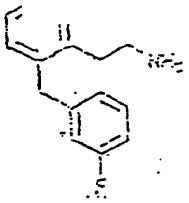
Verbindung 126



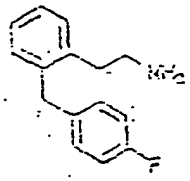
Verbindung 127



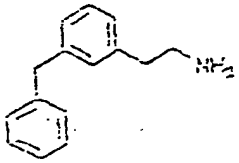
Verbindung 129



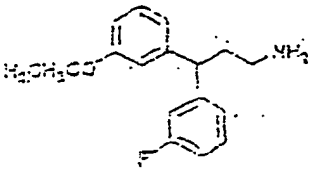
Verbindung 130



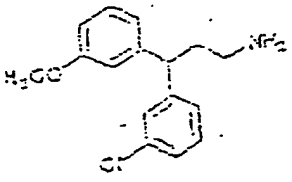
Verbindung 131



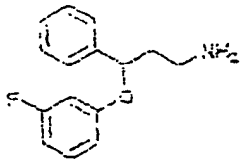
Verbindung 134



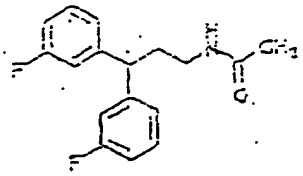
Verbindung 135



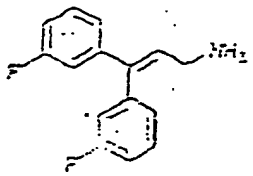
Verbindung 136



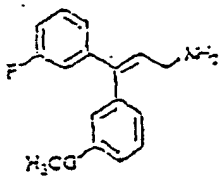
Verbindung 137



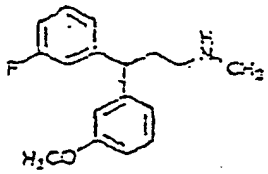
Verbindung 138



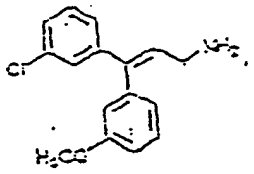
Verbindung 139



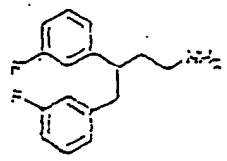
Verbindung 141



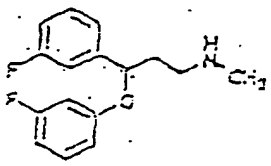
Verbindung 142



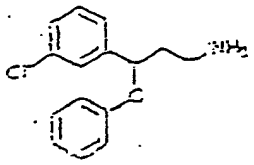
Verbindung 143



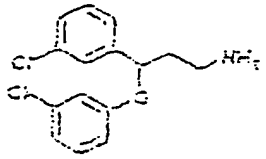
Verbindung 144



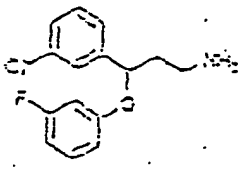
Verbindung 145



Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen davon.

23. Verbindung gemäß Anspruch 22, die aus den Verbindungen 54-66, 69, 76, 82, 83, 88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131,135-139, 142, 144, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

24. Verbindung gemäß Anspruch 22, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150 oder. pharmazeutisch verträglichen Salzen davon ausgewählt ist.

25. Verbindung gemäß Anspruch 22, die aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

26. Verbindung gemäß Anspruch 22, die aus den Verbindungen 118-122, 137, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

27. Verbindung gemäß Anspruch 22, die aus den Verbindungen 118-122, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

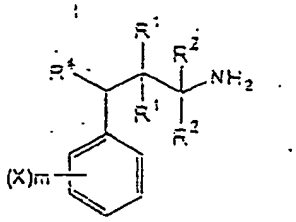
28. Verbindung gemäß Anspruch 22, die aus den Verbindungen 63 und 64 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

29. Verbindung gemäß Anspruch 22, die aus der Verbindung 119 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

30. Verbindung gemäß Anspruch 22, die aus der Verbindung 144 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

31. Verbindung 60 oder pharmazeutisch verträgliche Salze davon.

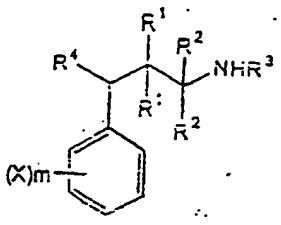
32. Verbindung der Formel:



wobei:

X unabhängig aus -Br, -Cl, -F, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl, -OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 1 bis 5 ist; und pharmazeutisch verträgliche Salze und Komplexe davon.

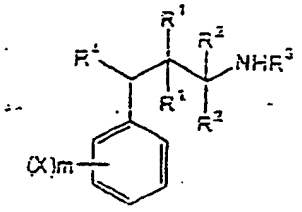
33. Verbindung der Formel:



wobei:

X unabhängig aus -F, -Cl, -Br, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem-O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem C_{1-4}-Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 1 bis 5 ist; und pharmazeutisch verträgliche Salze und Komplexe davon mit der Maßgabe, dass die Verbindung nicht N-Methyl-3-(m-trifluormethylphenoxy)-3-(4-fluorphenyl)propylamin ist.

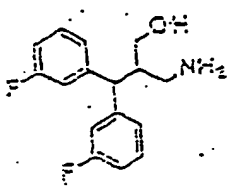
34. Verbindung der Formel:



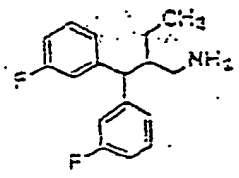
wobei:

(X)m aus einem meta-Fluor-, meta-Chloratom, ortho-O-C_{1-4}-Alkylrest, einer ortho-Methylgruppe, einem ortho-Fluor-, ortho-Chloratom, meta-O-C_{1-4}-Alkylrest, einer meta-Methylgruppe, ortho-OH und meta-OH ausgewählt ist;
R_1 H ist;
R_2 H ist;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, einem Alkyl, -OH. $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
pharmazeutisch verträgliche Salze und Komplexe davon.

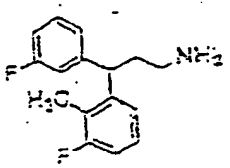
35. Arzneimittel, umfassend eine Verbindung, welche aus



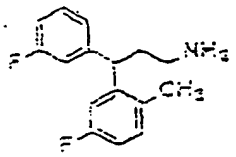
Verbindung 54



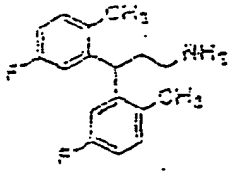
Verbindung 55



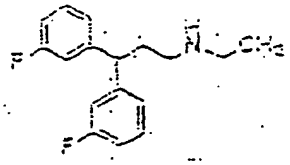
Verbindung 56



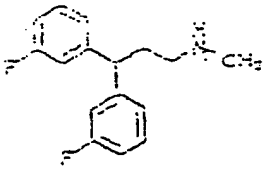
Verbindung 57



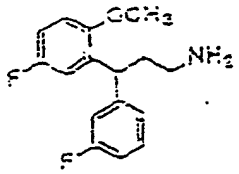
Verbindung 58



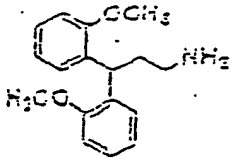
Verbindung 59



Verbindung 60



Verbindung 61



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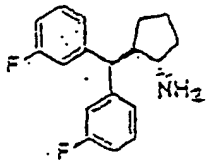

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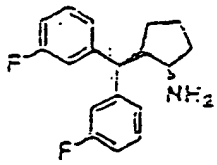

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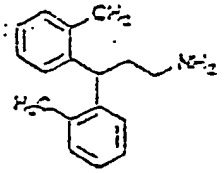

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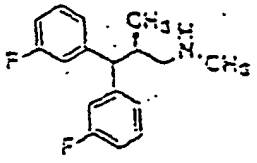

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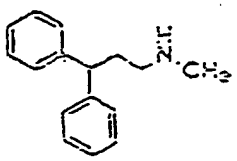

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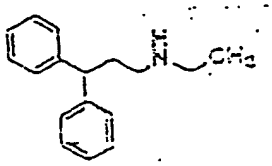

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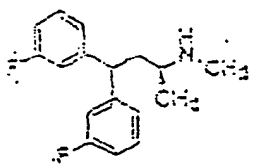
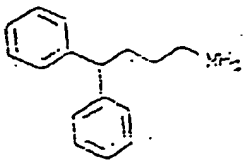


Verbindung 69



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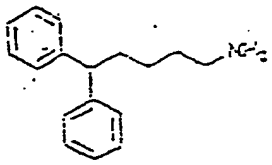
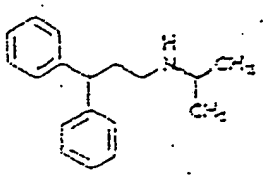
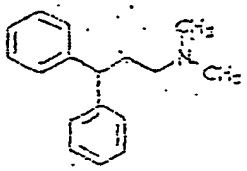


Verbindung 71



Verbindung 72



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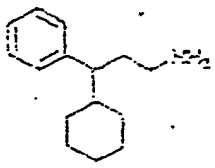

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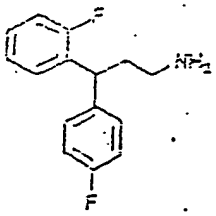

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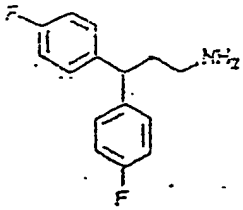
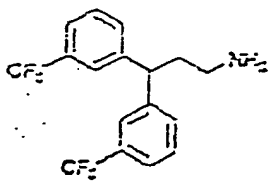


Verbindung 77



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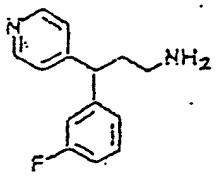

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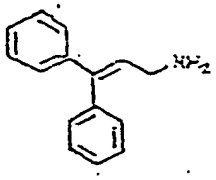
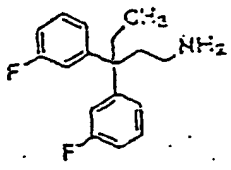
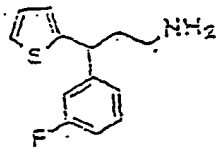


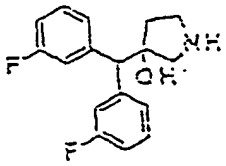
Verbindung 81



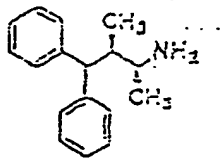
Verbindung 82

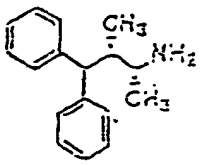


Verbindung 83

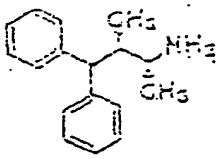


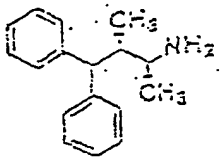
Verbindung 84



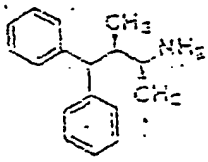


Verbindung 85
(Gemisch aus 2
Verbindungen)

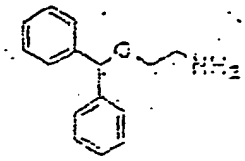




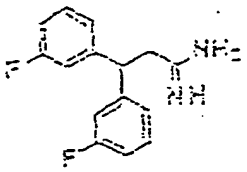
Verbindung 86
(Gemisch aus 2
Verbindungen)



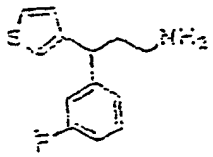
Verbindung 87



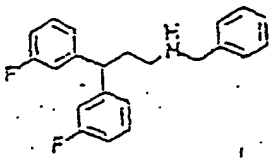
Verbindung 88



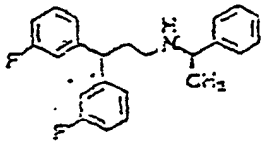
Verbindung 89



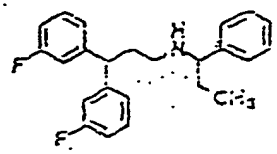
Verbindung 90



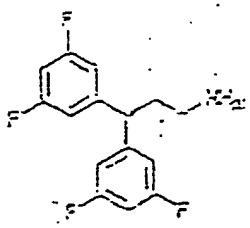
Verbindung 92



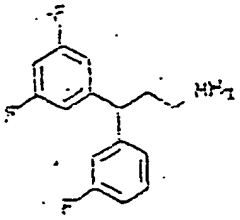
Verbindung 93



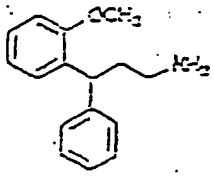
Verbindung 94



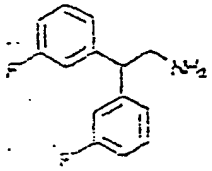
Verbindung 95



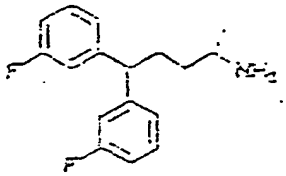
Verbindung 96



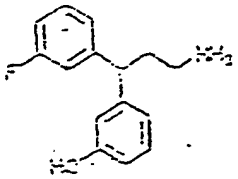
Verbindung 97



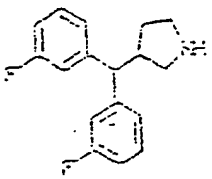
Verbindung 98



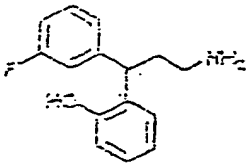
Verbindung 100



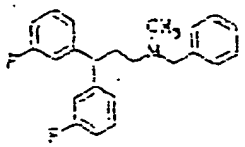
Verbindung 101



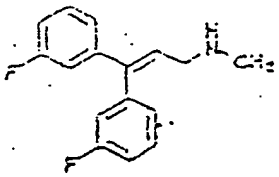
Verbindung 102



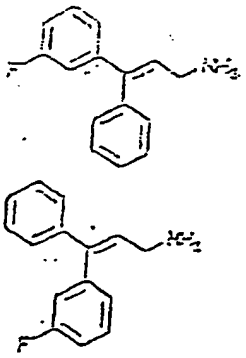
Verbindung 103



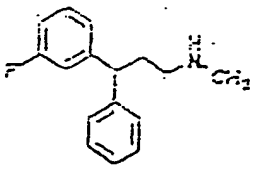
Verbindung 105



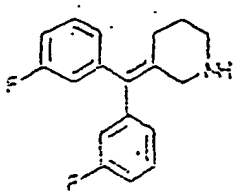
Verbindung 106



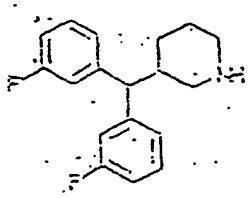
Verbindung 107
(Gemisch aus 2
Verbindungen)



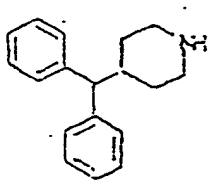
Verbindung 108



Verbindung 109



Verbindung 111



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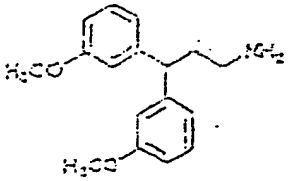

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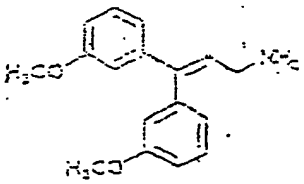

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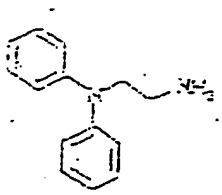

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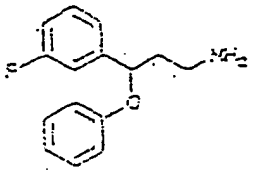

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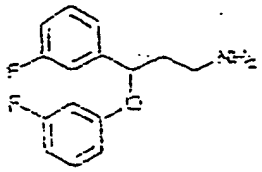
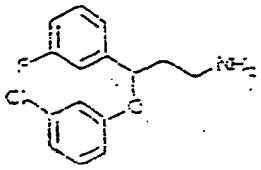
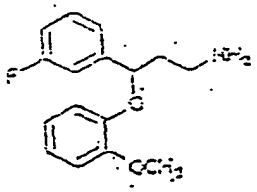


Verbindung 119



Verbindung 120



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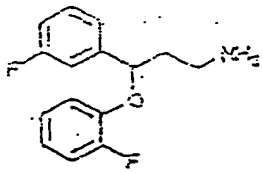

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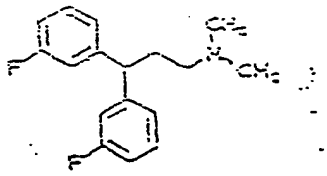

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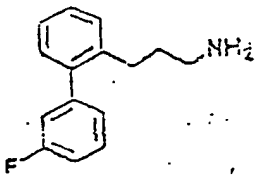

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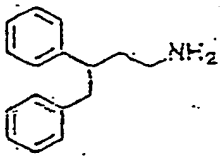

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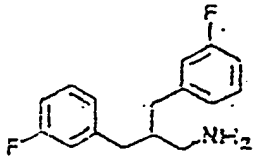
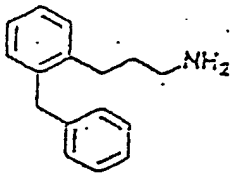


Verbindung 126



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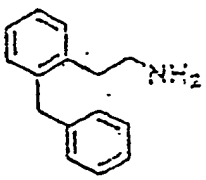

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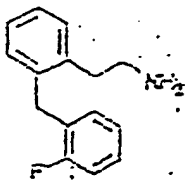

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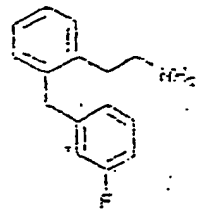

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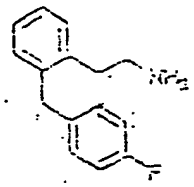

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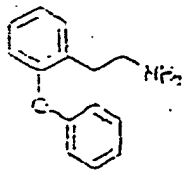

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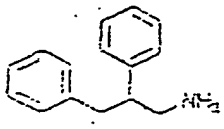

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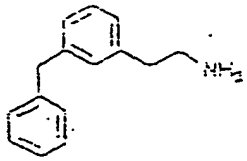

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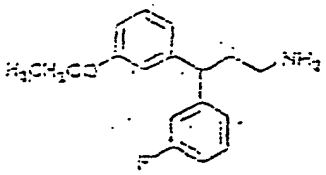

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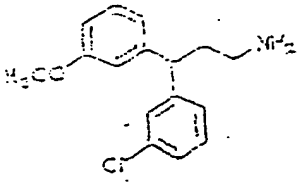

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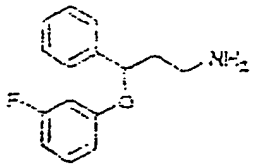

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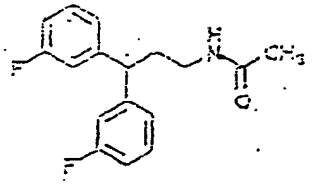

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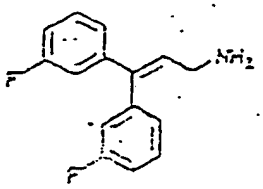

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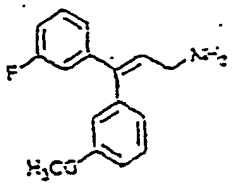

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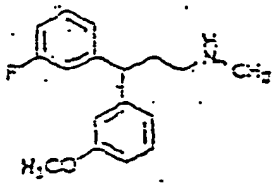

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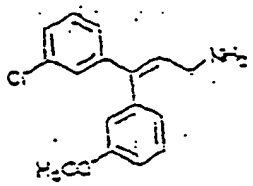

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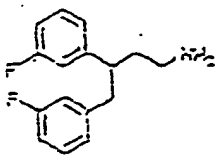
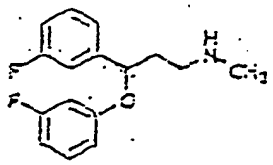


Verbindung 144



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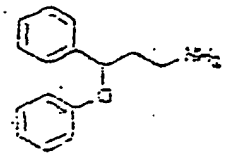

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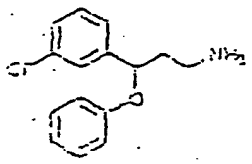
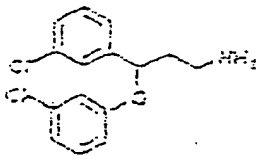
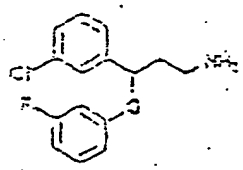


Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen davon ausgewählt ist in einem pharmazeutisch verträglichen Träger.

36. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

37. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

38. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

39. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

40. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

41. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

42. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 118-122, 137, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

43. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 118-122, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

44. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 63 und 64 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

45. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus der Verbindung 119 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

46. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus der Verbindung 144 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

47. Arzneimittel umfassend eine Verbindung, die aus der Verbindung 60 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

48. Arzneimittel umfassend eine Verbindung gemäß Anspruch 32 in einem pharmazeutisch verträglichen Träger.

49. Arzneimittel umfassend eine Verbindung gemäß Anspruch 33 in einem pharmazeutisch verträglichen Träger.

50. Arzneimittel umfassend eine Verbindung gemäß Anspruch 34 in einem pharmazeutisch verträglichen Träger.

51. Arzneimittel gemäß einem der Ansprüche 35-50, das an die Behandlung von neurologischen Krankheiten und Störungen angepasst ist.

52. Arzneimittel gemäß Anspruch 51, wobei die neurologische Krankheit oder Störung aus Schlaganfall, Schädeltrauma, Rückenmarksverletzung, Epilepsie, Ängstlichkeit, Alzheimer-Krankheit, Chorea Huntington, Parkinson-Krankheit oder amyotrophische Lateralsklerose ausgewählt ist.

53. Arzneimittel gemäß Anspruch 51, wobei das Arzneimittel neuroprotektive Wirkung aufweist.

54. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall als Totalischämie auftritt.

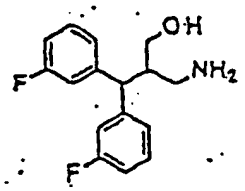
55. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall als fokale Ischämie auftritt.

56. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall in hemorrhagischer Form auftritt.

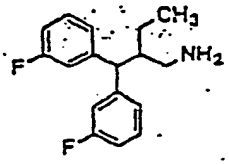
57. Arzneimittel gemäß Anspruch 52, wobei die neurologische Krankheit oder Störung Parkinson-Krankheit ist.

Revendications

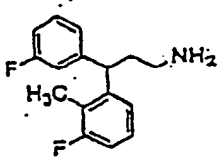
1. Utilisation d'un composé qui est choisi dans le groupe consistant en :



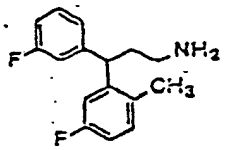
Composé 54



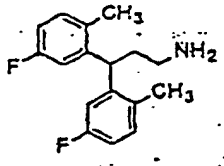
Composé 55



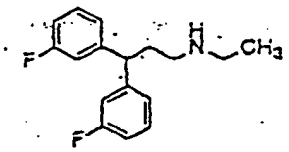
Composé 56



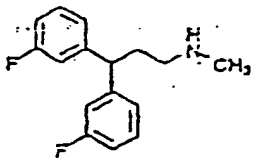
Composé 57



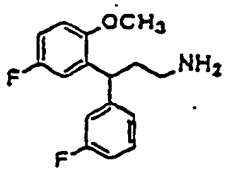
Composé 58



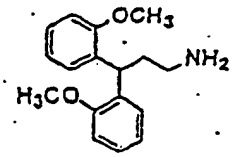
Composé 59



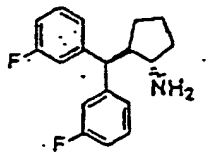
Composé 60



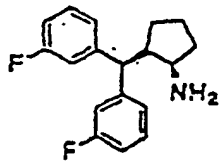
Composé 61



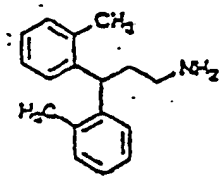
Composé 62



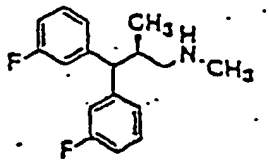
Composé 63



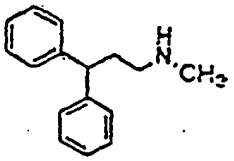
Composé 64



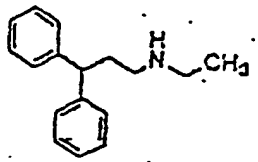
Composé 65



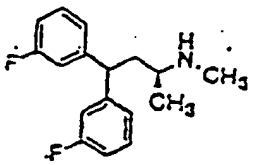
Composé 66



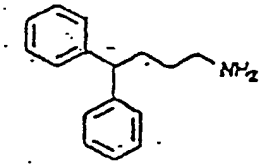
Composé 67



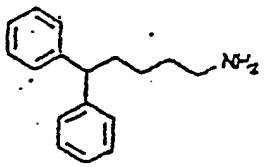
Composé 68



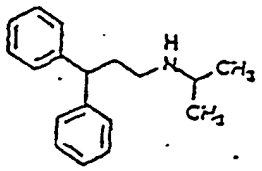
Composé 69



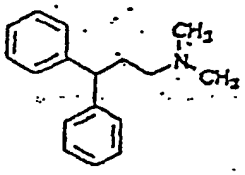
Composé 70



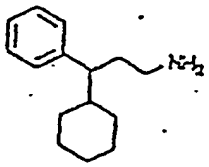
Composé 71



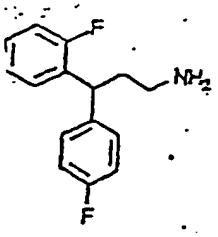
Composé 72



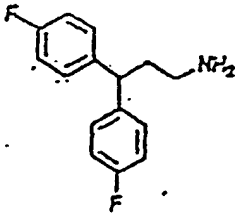
Composé 73



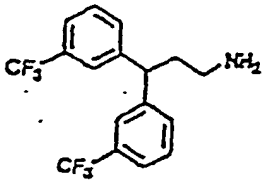
Composé 75



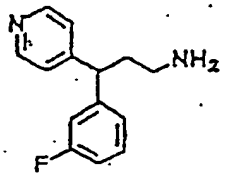
Composé 76



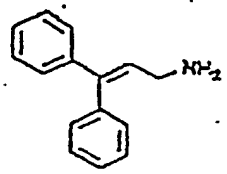
Composé 77



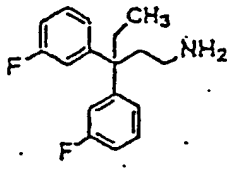
Composé 78



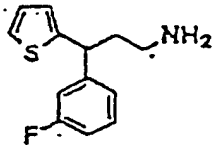
Composé 79



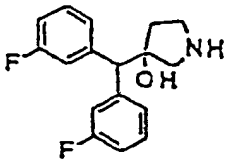
Composé 81



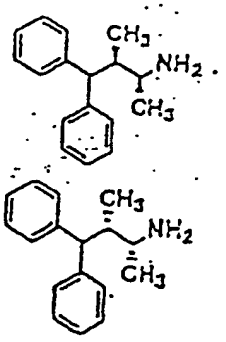
Composé 82



Composé 83

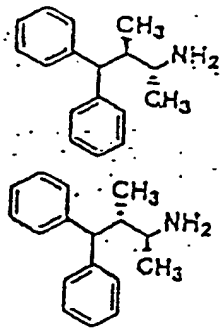


Composé 84



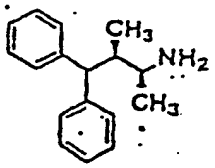
Composé 85

(Mélange de 2 composés)

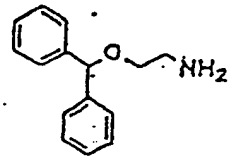


Composé 86

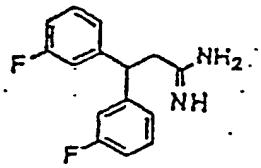
(Mélange de 2 composés)



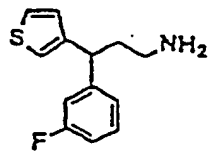
Composé 87



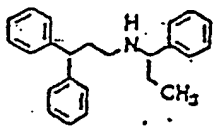
Composé 88



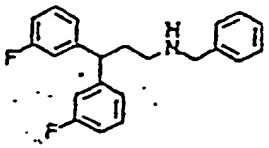
Composé 89



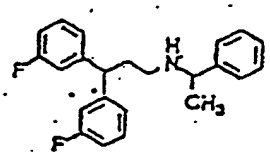
Composé 90



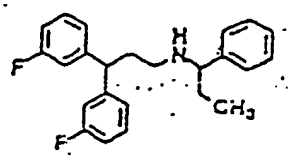
Composé 91



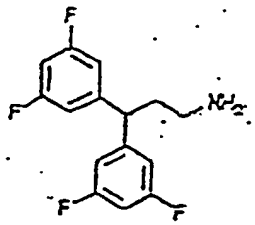
Composé 92



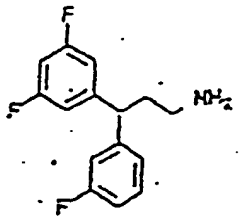
Composé 93



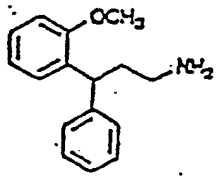
Composé 94



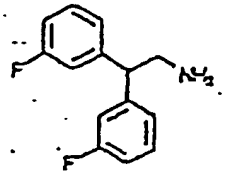
Composé 95



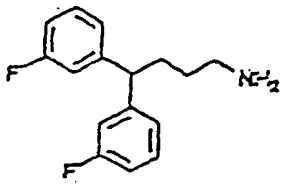
Composé 96



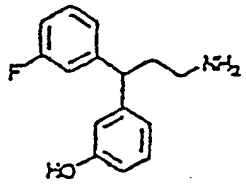
Composé 97



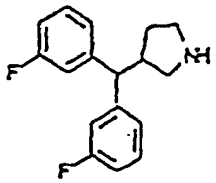
Composé 98



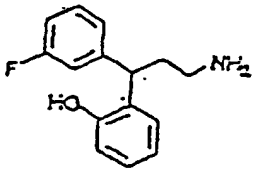
Composé 100



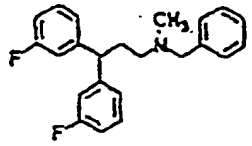
Composé 101



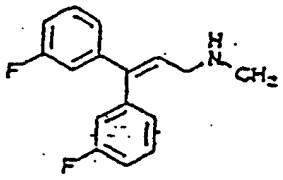
Composé 102



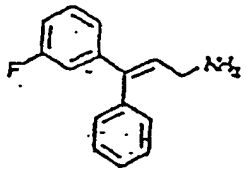
Composé 103

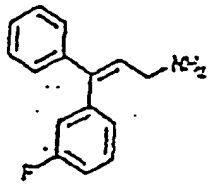


Composé 105



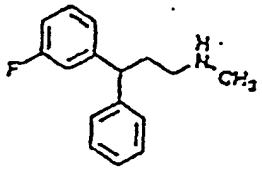
Composé 106



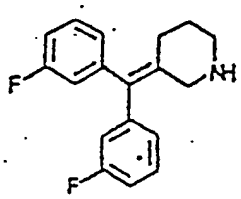


Composé 107

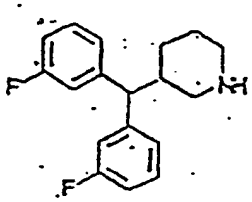
(Mélange de 2 composés)



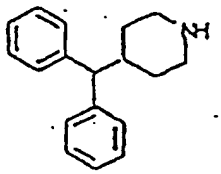
Composé 108



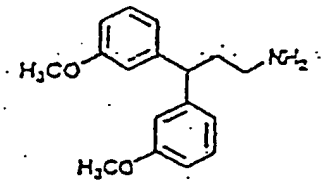
Composé 109



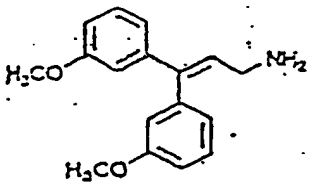
Composé 111



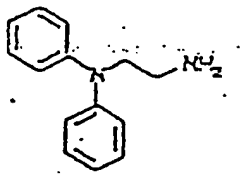
Composé 114



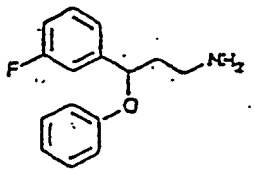
Composé 115



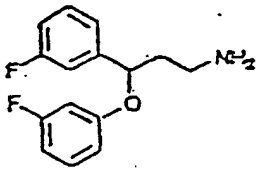
Composé 116



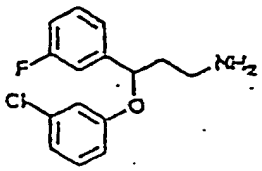
Composé 117



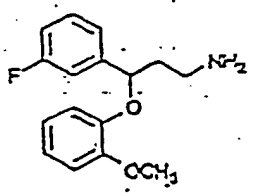
Composé 118



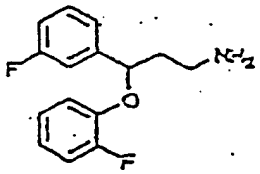
Composé 119



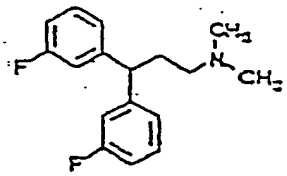
Composé 120



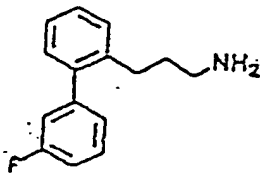
Composé 121



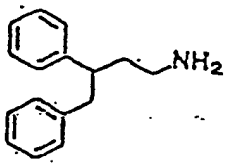
Composé 122



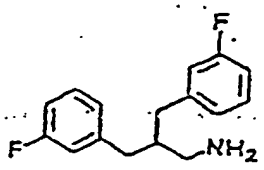
Composé 123



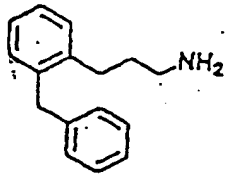
Composé 124



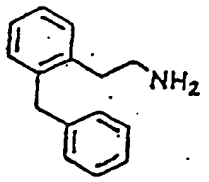
Composé 125



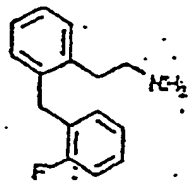
Composé 126



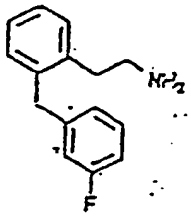
Composé 127



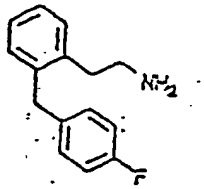
Composé 128



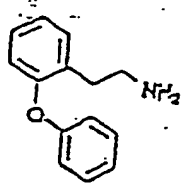
Composé 129



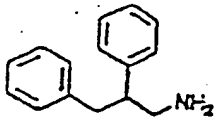
Composé 130



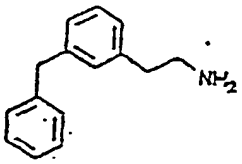
Composé 131



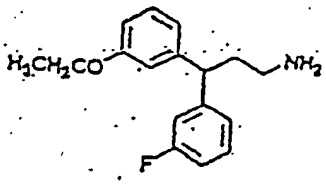
Composé 132



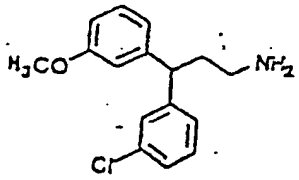
Composé 133



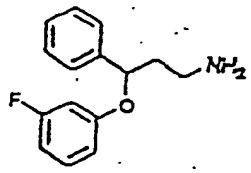
Composé 134



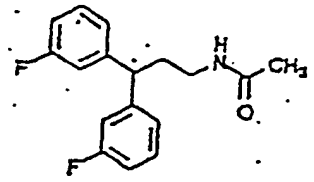
Composé 135



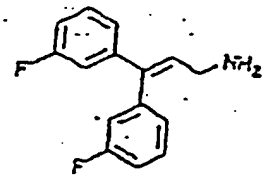
Composé 136



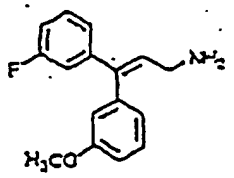
Composé 137



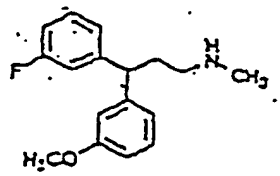
Composé 138



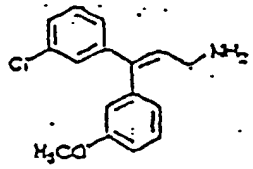
Composé 139



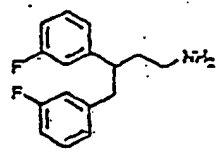
Composé 141



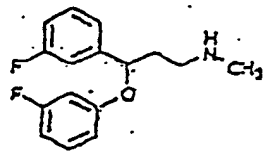
Composé 142



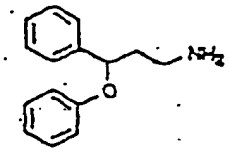
Composé 143



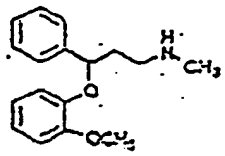
Composé 144



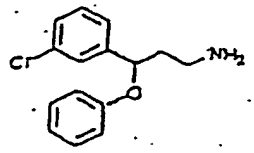
Composé 145



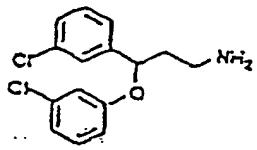
Composé 146



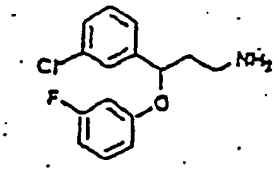
Composé 147



Composé 148



Composé 149



Composé 150

et leurs sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

2. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

3. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150, et leurs sels et complexes pharmaceutiquement acceptables.

4. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

5. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150, et leurs sels et complexes pharmaceutiquement acceptables.

6. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89-90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

7. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

8. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 118-122, 137, 145, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

9. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 118-122, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

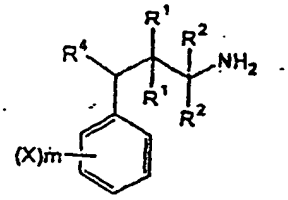
10. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 63 et 64 et leurs sels et complexes pharmaceutiquement acceptables.

11. Utilisation selon la revendication 1, dans laquelle le composé est choisi parmi le composé 119 et ses sels et complexes pharmaceutiquement acceptables.

12. Utilisation selon la revendication 1, dans laquelle le composé est choisi parmi le composé 144 et ses sels et complexes pharmaceutiquement acceptables.

13. Utilisation du composé 60 et de ses sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

14. Utilisation d'un composé de formule :



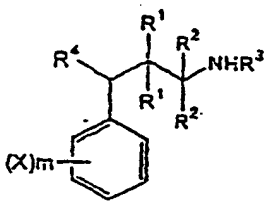
dans laquelle :

X est choisi indépendamment dans le groupe consistant en -Br, -Cl, -F, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et -Oacyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-O-CF_3$, -O-alkyle et -O-acyle ; et m est indépendamment un nombre entier de 0 à 5 ; et ses sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas :

3-(p-isopropoxyphénoxy)-3-phénylpropylamine
3-(2'-methyl-4',5'-dichlorophénoxy)-3-phénylpropylamine
3-(p-tert-butylphénoxy)-3-phénylpropylamine
3-(2',4'-dichlorophénoxy)-3-phényl-2-méthylpropylamine
3-(o-éthylphénoxy)-3-phénylpropylamine
3-(o-méthoxyphénoxy)-3-phénylpropylamine
3-phénoxy-3-phénylpropylamine

pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

15. Utilisation d'un composé de formule :



dans laquelle :

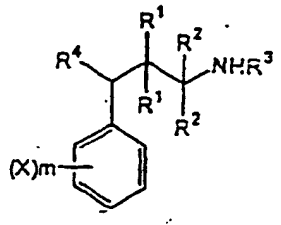
X est choisi indépendamment dans le groupe consistant en -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle et -O-acyle ; et m est indépendamment un nombre entier de 0 à 5 ; et leurs sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas :

N-méthyl 3-(o-chloro-p-tolyloxy)-3-phényl-1-méthylpropylamine
N-méthyl 3-(p-tolyloxy)-3-phénylpropylamine

N-méthyl 3-(o-chloro-p-isopropylphénoxy)-3-phényl-2-méthylpropylamine
N-méthyl 3-(p-iodophénoxy)-3-phényl-propylamine
N-méthyl 3-(3-n propylphénoxy)-3-phénylpropylamine
N-méthyl 3-(p-trifluorométhylphénoxy)-3-phénylpropylamine
N-méthyl 3-(m-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(p-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-(p-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-tolyloxy)-3-phénylpropylamine
N-méthyl 3-(p-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(m-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-phénoxy-3 -phényl-2-méthylpropylamine
N-méthyl 3-phénoxy-3-phényl-1-méthylpropylamine
N-méthyl 3-phénoxy-3-phénylpropylamine
N-méthyl 3-(o-trifluorométhylphénoxy)-3-phénylpropylamine
N-méthyl 3-(m-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o,p-difluorophénoxy)-3-phénylpropylamine
N-éthyl 3-(o-iodophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-bromophénoxy)-3-phénylpropylamine

pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

16. Utilisation d'un composé de formule :



dans laquelle :

(X)m est choisi dans le groupe consistant en méta-fluoro, méta-chloro, ortho-O-C_1-C_4 alkyle, ortho-méthyle, ortho-fluoro, ortho-chloro, méta-O-C_1-C_4 alkyle, métaméthyle, ortho-OH et méta-OH ;
R_1 est H;
R_2 est H;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, -CF_3, alkyle, -OH,-OCF_3, -O-alkyle et -O-acyle ;

et ses sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

17. Utilisation selon l'une quelconque des revendications 1 à 6, dans laquelle la maladie ou le désordre comprend un accident vasculaire cérébral, un traumatisme crânien, une lésion de la moelle épinière, une ischémie de la moelle épinière, un dommage neuronal induit par une ischémie ou une hypoxie, l'épilepsie, la douleur, l'anxiété, des déficits neuropsychiatriques ou cognitifs dus à une ischémie ou une hypoxie tels que ceux survenant fréquemment en tant que conséquence d'une opération chirurgicale cardiaque sous dérivation cardio-pulmonaire, la maladie d'Alzheimer, la maladie de Huntington, la maladie de Parkinson, ou la sclérose amyotrophique latérale.

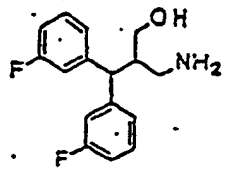
18. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature ischémique global.

19. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature ischémique focal.

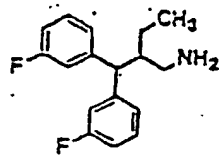
20. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature hémmoragique.

21. Utilisation selon la revendication 17, dans laquelle la maladie ou le désordre neurologique comprend la maladie de Parkinson.

22. Composé choisi dans le groupe consistant en :



Composé 54



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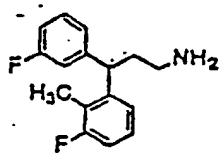

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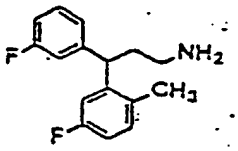

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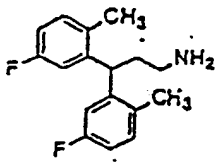
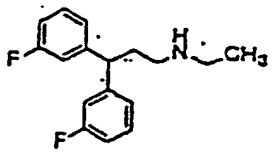


Composé 58



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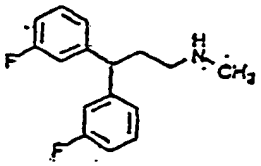

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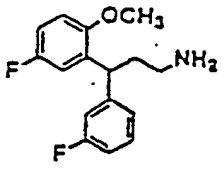

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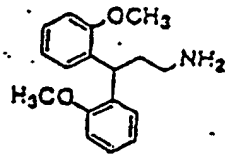

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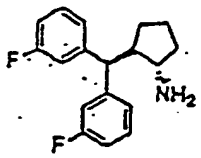
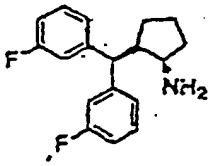


Composé 63



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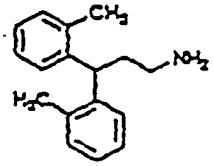

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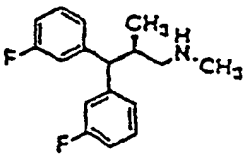

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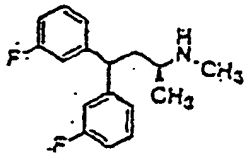
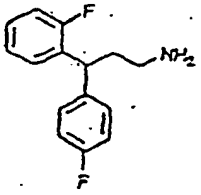
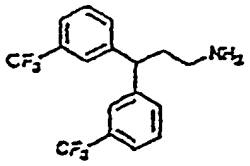


Composé 69



Composé 75



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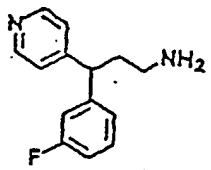

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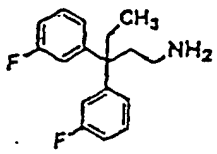

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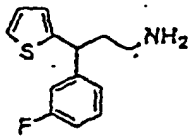

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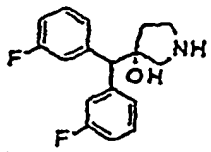
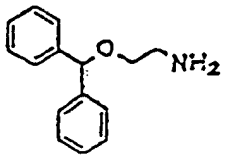


Composé 84



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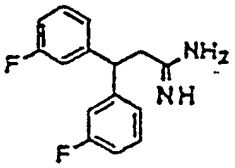

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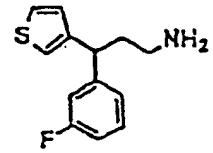

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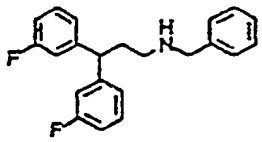

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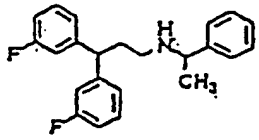

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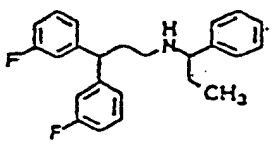
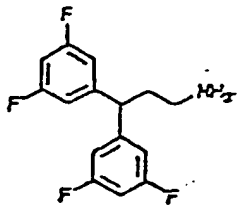
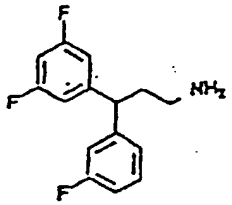


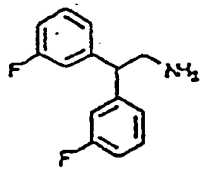
Composé 94



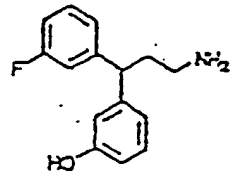
Composé 95



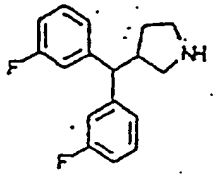
Composé 96



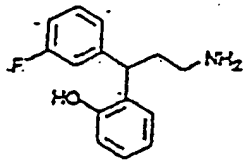
Composé 98



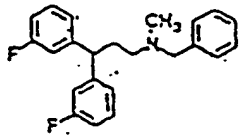
Composé 101



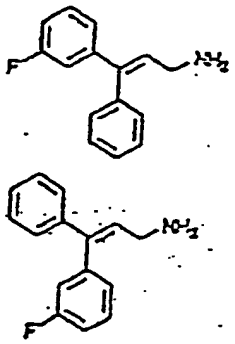
Composé 102



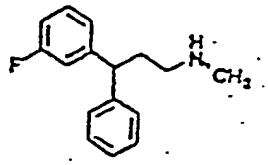
Composé 103



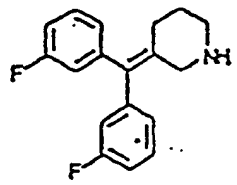
Composé 105



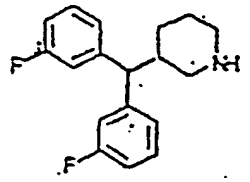
Composé 107
(Mélange de 2 composés)



Composé 108



Composé 109



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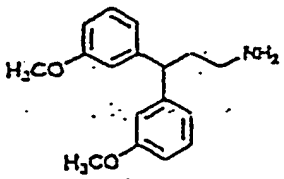
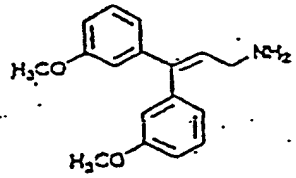
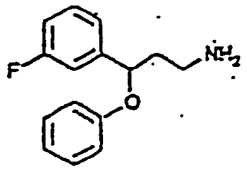


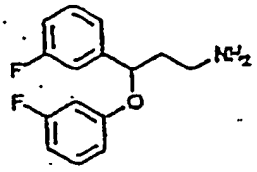
Composé 115



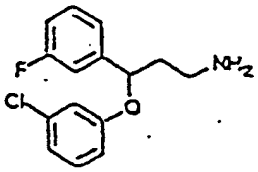
Composé 116



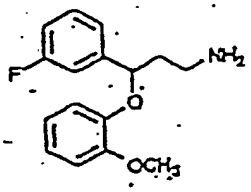
Composé 118



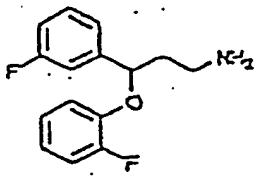
Composé 119



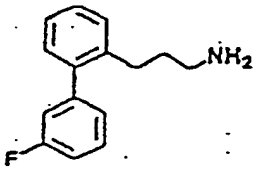
Composé 120



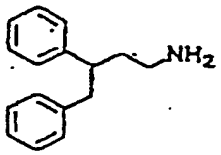
Composé 121



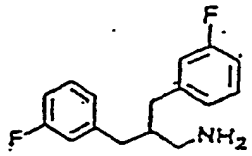
Composé 122



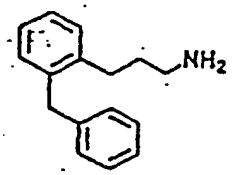
Composé 124



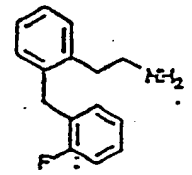
Composé 125



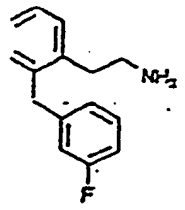
Composé 126



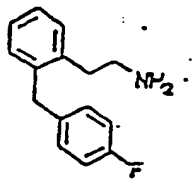
Composé 127



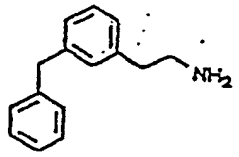
Composé 129



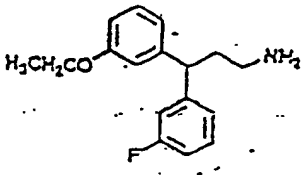
Composé 130



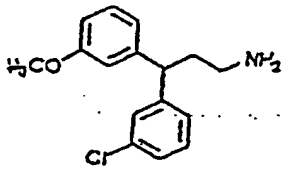
Composé 131



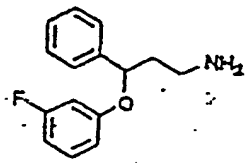
Composé 134



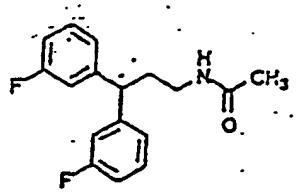
Composé 135



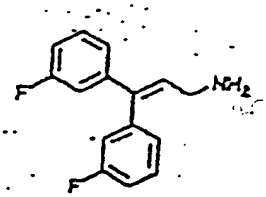
Composé 136



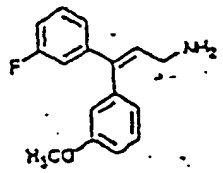
Composé 137



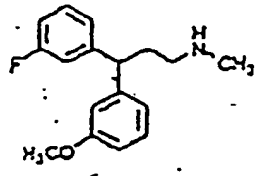
Composé 138



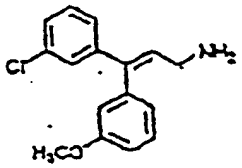
Composé 139



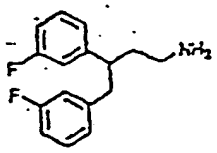
Composé 141



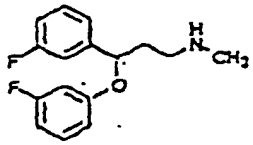
Composé 142



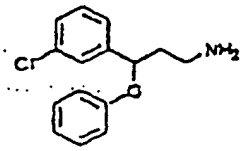
Composé 143



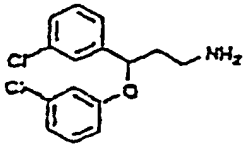
Composé 144



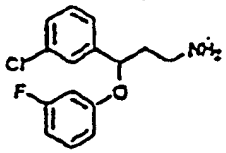
Composé 145



Composé 148



Composé 149



Composé 150

et leurs sels pharmaceutiquement acceptables.

23. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 54-66, 69, 76, 82, 83, 88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131, 135-139, 142, 144, 145, 148-150, ou leurs sels pharmaceutiquement acceptables.

24. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

25. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 60-66, 69, 70, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

26. Composé selon la revendication 22 choisi dans le groupe consistant en les composés, 118-122, 137, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

27. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 118-122, 148-150, ou ses sels pharmaceutiquement acceptables.

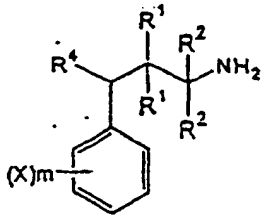
28. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 63 et 64 ou ses sels pharmaceutiquement acceptables.

29. Composé selon la revendication 22 choisi parmi le composé 119 ou ses sels pharmaceutiquement acceptables.

30. Composé selon la revendication 22 choisi parmi le composé 144 ou ses sels pharmaceutiquement acceptables.

31. Composé 60 ou ses sels pharmaceutiquement acceptables.

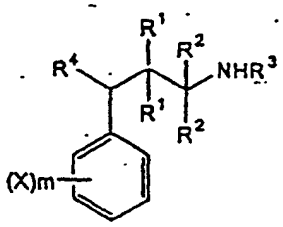
32. Composé de formule :



dans laquelle :

X est choisi indépendamment dans le groupe consistant en -Br, -Cl, -F, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle et -O-acyle ; et
m est indépendamment un nombre entier de 1 à 5 ; et ses sels et complexes pharmaceutiquement acceptables

33. Composé de formule :

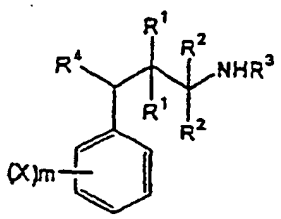


dans laquelle :

X est choisi indépendamment dans le groupe consistant en -F, -Cl, -Br,-I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;

R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle ou-O-acyle ; et m est indépendamment un nombre entier de 1 à 5 ; et ses sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas N-méthyl 3-(m-trifluorométhylphénoxy)-3-(4-fluorophényl)propylamine.

34. Composé de formule :

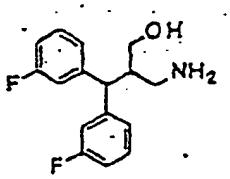


dans laquelle :

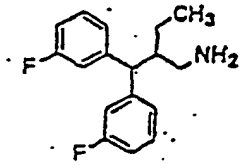
(X)m est choisi dans le groupe consistant en méta-fluoro, méta-chloro, ortho-O-C_1-C_4 alkyle, ortho-méthyle, ortho-fluoro, ortho-chloro, méta-O- C_1-C_4 alkyle, métaméthyle, ortho-OH et méta-OH ;
R_1 est H;
R_2 est H;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle ou-O-acyle ;

et ses sels et complexes pharmaceutiquement acceptables.

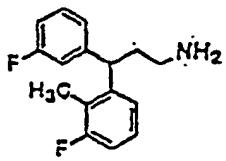
35. Composition pharmaceutique comprenant un composé choisi dans le groupe consistant en



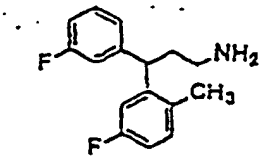
Composé 54



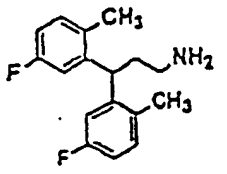
Composé 55



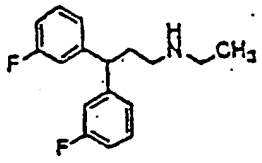
Composé 56



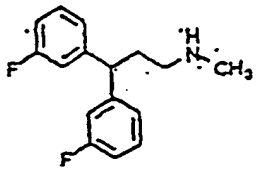
Composé 57



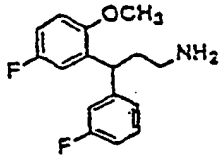
Composé 58



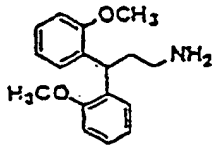
Composé 59



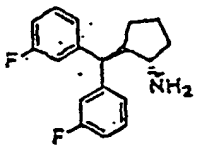
Composé 60



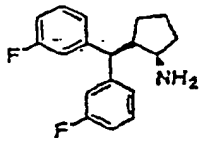
Composé 61



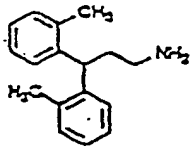
Composé 62



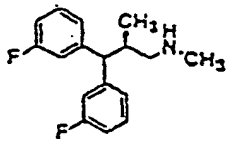
Composé 63



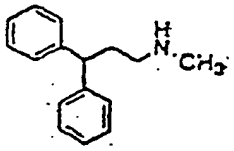
Composé 64



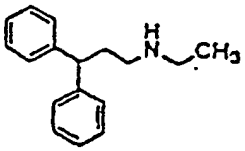
Composé 65



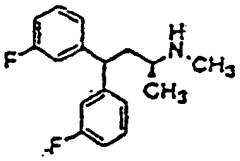
Composé 66



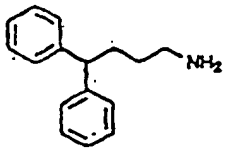
Composé 67



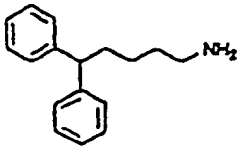
Composé 68



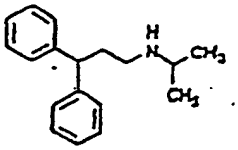
Composé 69



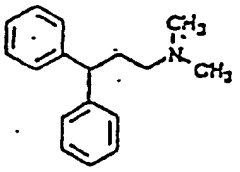
Composé 70



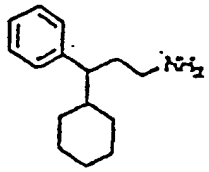
Composé 71



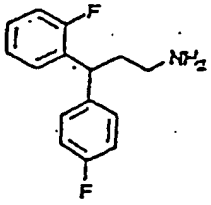
Composé 72



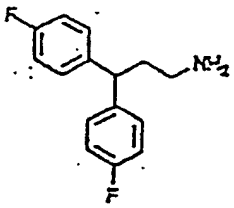
Composé 73



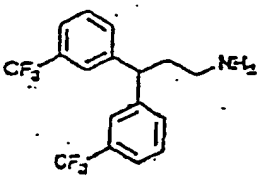
Composé 75



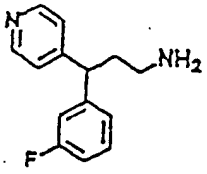
Composé 76



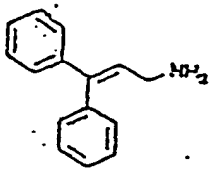
Composé 77



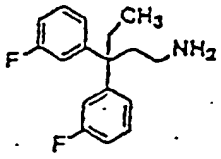
Composé 78



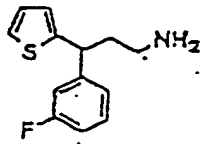
Composé 79



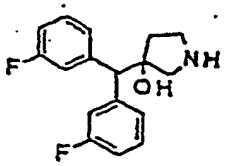
Composé 81



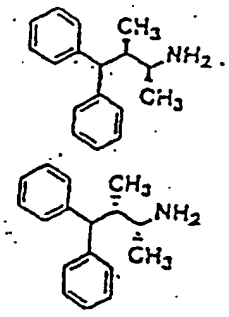
Composé 82



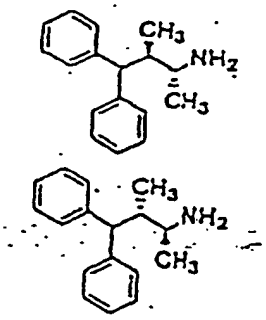
Composé 83



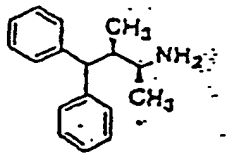
Composé 84



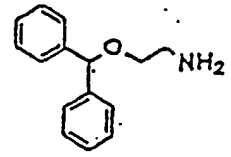
Composé 85
(Mélange de 2 composés)



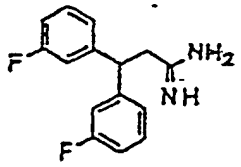
Composé 86
(Mélange de 2 composés)



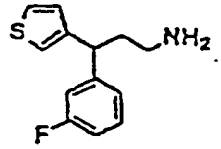
Composé 87



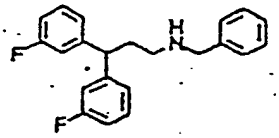
Composé 88



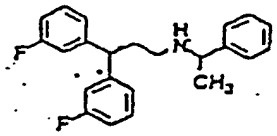
Composé 89



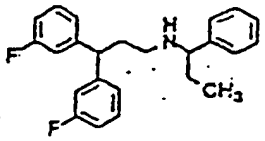
Composé 90



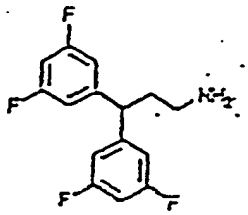
Composé 92



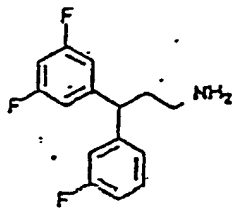
Composé 93



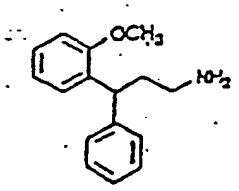
Composé 94



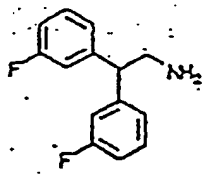
Composé 95



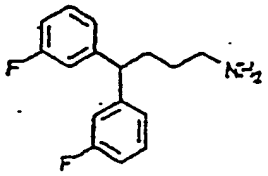
Composé 96



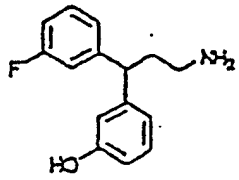
Composé 97



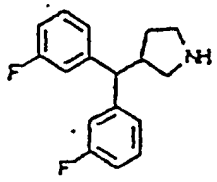
Composé 98



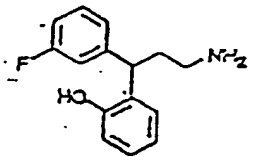
Composé 100



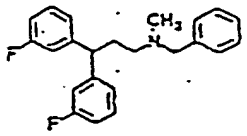
Composé 101



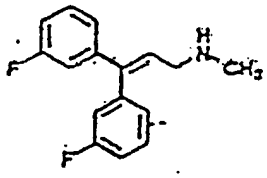
Composé 102



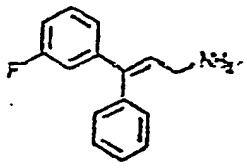
Composé 103

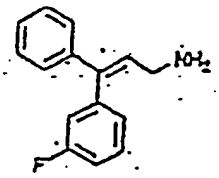


Composé 105



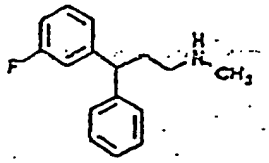
Composé 106



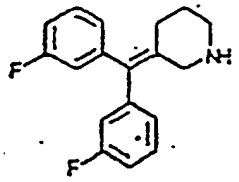


Composé 107

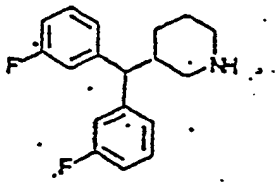
(Mélangé de 2 composés).



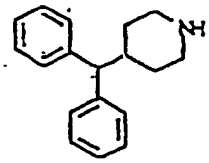
Composé 108



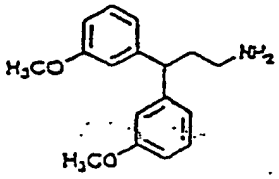
Composé 109



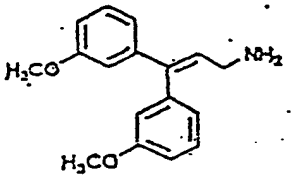
Composé 111



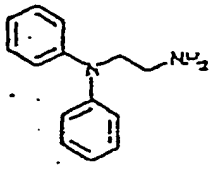
Composé 114



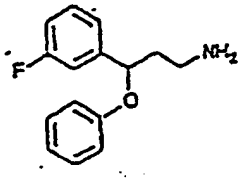
Composé 115



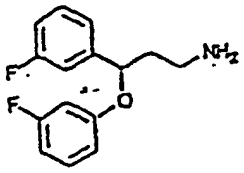
Composé 116



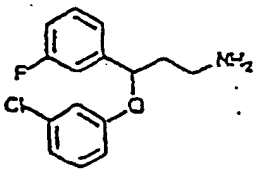
Composé 117



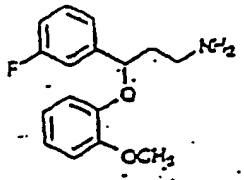
Composé 118



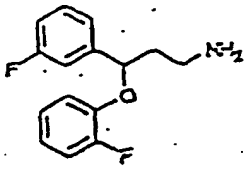
Composé 119



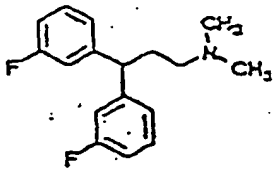
Composé 120



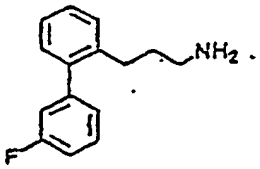
Composé 121



Composé 122



Composé 123



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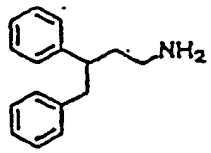

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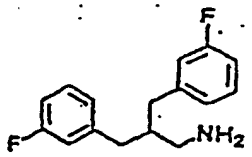

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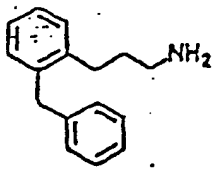

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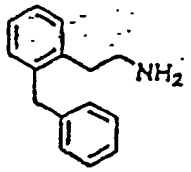

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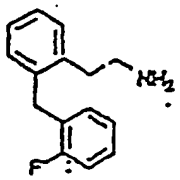

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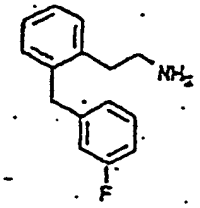

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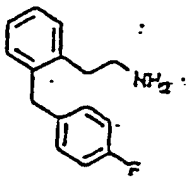

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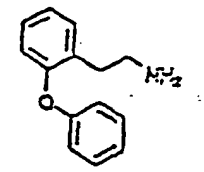

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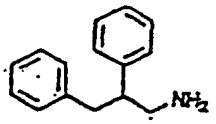

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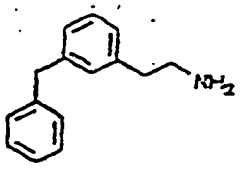

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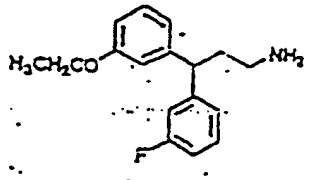

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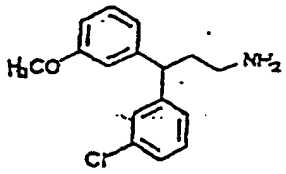

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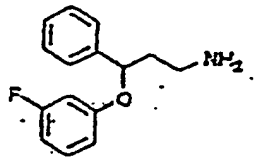

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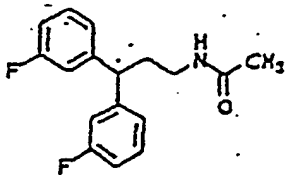

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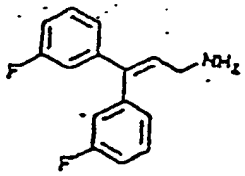

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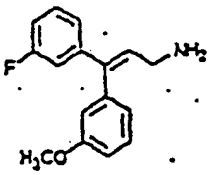

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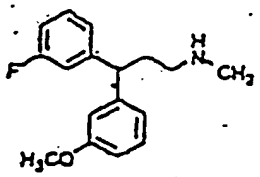

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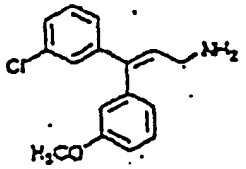

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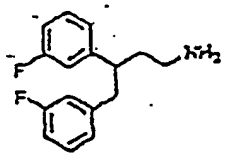

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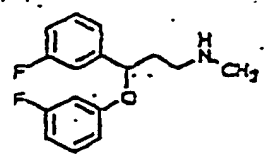

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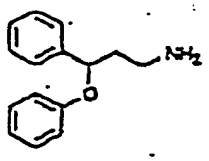

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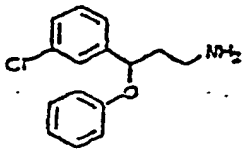

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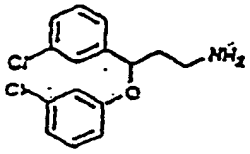

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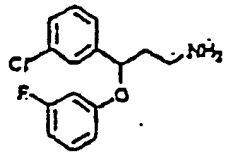


Composé 150

et leurs sels pharmaceutiquement acceptables dans un véhicule pharmaceutiquement acceptable.

36. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

37. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

38. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

39. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-97; 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

40. Composition pharmaceutique selon la revendication -35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

41. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

42. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 118-122, 137, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

43. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 118-122, 148-150, et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

44. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 63 et 64 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

45. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 119 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

46. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 144 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

47. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 60 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

48. Composition pharmaceutique comprenant un composé selon la revendication 32, dans un véhicule pharmaceutiquement acceptable.

49. Composition pharmaceutique comprenant un composé selon la revendication 33, dans un véhicule pharmaceutiquement acceptable.

50. Composition pharmaceutique comprenant un composé selon la revendication 34, dans un véhicule pharmaceutiquement acceptable.

51. Composition pharmaceutique selon l'une quelconque des revendication 35-50, adaptée au traitement d'une maladie ou d'un désordre neurologique.

52. Composition pharmaceutique selon la revendication 51, dans laquelle la maladie ou le désordre est choisi dans le groupe consistant en un accident vasculaire cérébral, un traumatisme crânien, une lésion de la moelle épinière, l'épilepsie, l'anxiété, la maladie d'Alzheimer, la maladie de Huntington, la maladie de Parkinson, ou la sclérose amyotrophique latérale.

53. Composition pharmaceutique selon la revendication 51, dans laquelle la composition pharmaceutique a une activité neuro-protectrice.

54. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature ischémique globale.

55. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature ischémique focale.

56. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature hémorragique.

57. Composition pharmaceutique selon la revendication 52, dans laquelle.la maladie ou le désordre neurologique est la maladie de Parkinson.

Erteilt auf Grund des Ersten Überleitungsgesetzes vom 8. Juli 1949
(WiGBl. S. 175)

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
4. FEBRUAR 1952

DEUTSCHES PATENTAMT

PATENTSCHRIFT

Nr. 830 193

KLASSE 12p GRUPPE 5

p 21280 IV c/12 p D

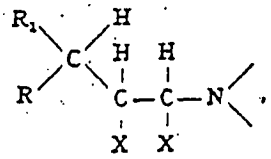
Dr. Gustav Ehrhart, Frankfurt/M.-Unterliederbach und
Dr. Walter Bestian, Frankfurt/M.-Zeilsheim
sind als Erfinder genannt worden

Farbwerke Hoechst, vormals Meister Lucius & Brüning,
Frankfurt/M.-Höchst

Verfahren zur Herstellung von basischen Verbindungen

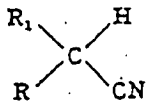
Patentiert im Gebiet der Bundesrepublik Deutschland vom 10. November 1948 an
Patenterteilung bekanntgemacht am 3. Januar 1952

Es wurde gefunden, daß Verbindungen der allgemeinen Formel

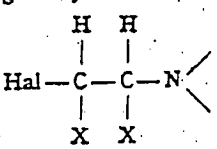


wobei R einen aromatischen und R_1 einen heterocyclischen Rest und X Wasserstoff oder Methyl bedeuten und N ein tertiär gebundenes Stickstoffatom ist, Spasmolytica darstellen, die sich insbesondere durch eine hervorragende Wirkung beim Histaminkrampf auszeichnen.

Zweckmäßig stellt man diese Verbindungen aus Nitrilen der allgemeinen Formel



her, wobei R einen aromatischen und R_1 einen heterocyclischen Rest bedeuten, auf die man in Gegenwart von Natriumamid oder anderen halogenwasserstoffabspaltenden Mitteln ein basisch substituiertes Halogenalkyl der Formel



einwirken läßt. Solche Halogenide sind z. B. N-β-

Chloräthyldimethylamin, N-β-Chloräthyldiäthylamin, 1-Chlor-2-dimethylaminopropan, N-β-Chloräthylpiperidin, N-β-Chloräthylpyrrolidin und N-β-Chloräthylmorpholin. Durch weitere Einwirkung von Grignardreagens, Natriumamid und anderen kann die Cyangruppe unter Ersatz durch ein Wasserstoffatom abgespalten werden. Man kann aber auch die Cyangruppe mit verseifenden Mitteln behandeln, wobei die intermediär entstehenden Carbonsäuren unter Abspaltung von Kohlendioxyd ebenfalls in die gesuchten Verbindungen übergehen.

Beispiel 1

58,2 Gewichtsteile Phenylpyridyl-(2)-acetonitril vom F. = 84 bis 85°, bereitet aus Benzylcyanid, 2-Chlorpyridin und Natriumamid, werden in 300 Gewichtsteilen Toluol gelöst, mit 13 Gewichtsteilen Natriumamid umgesetzt und anschließend bei 30° mit einer Lösung von 36 Gewichtsteilen β-Chloräthyldimethylamin in 50 Gewichtsteilen Toluol versetzt. Bei 50 bis 60° erfolgt die Reaktion mit diesem Amin. Es wird 2 Stunden auf 100 bis 110° erwärmt, mit Wasser versetzt, die Toluollösung mit überschüssiger Essigsäure ausgezogen und der Auszug wieder alkalisch gemacht. Das so erhaltene Öl wird fraktioniert destilliert. In fast theoretischer Ausbeute geht das α-Phenyl-α-pyridyl-(2)-γ-dimethylaminobuttersäurenitril beim Destillieren unter 0,3 mm bei 150 bis 154° über.

In eine Grignard-Lösung aus 43,5 Gewichtsteilen Magnesium, 196 Gewichtsteilen Äthylbromid und 400 Gewichtsteilen Äther läßt man unter gleichzeitigem Abdestillieren des Äthers eine Lösung von 205 Gewichtsteilen α-Phenyl-α-pyridyl-(2)-γ-dimethylaminobuttersäurenitril in 400 Gewichtsteilen Benzol einfließen. Es wird 1 Stunde auf 80° erwärmt, danach mit Wasser-Salzsäure zersetzt und alkalisch gemacht. Das ausgeschiedene Öl ist das 1-Phenyl-1-pyridyl-(2')-3-dimethylaminopropan, das unter 0,3 mm bei 130 bis 135° siedet. Die Ausbeute entspricht fast der theoretischen Menge.

Beispiel 2

49 Gewichtsteile Phenylthiazolyl-(2)-acetonitril vom F. = 42 bis 44°, bereitet aus Benzylcyanid, 2-Chlorthiazol und Natriumamid, werden in 250 Gewichtsteilen Benzol mit 10,5 Gewichtsteilen Natriumamid und 26 Gewichtsteilen β-Chloräthyldimethylamin 1 Stunde auf 50 bis 60° und schließlich 2 Stunden auf 80 bis 85° erwärmt, mit Wasser behandelt, und die Benzollösung wird mit Essigsäure ausgezogen. Der Auszug wird alkalisch gemacht und das dabei erhaltene Öl destilliert. Das α-Phenyl-α-thiazolyl-(2)-γ-dimethylaminobuttersäurenitril siedet unter 0,3 mm bei 152 bis 155°.

9,5 Gewichtsteile Magnesium, 44 Gewichtsteile Äthylbromid und 150 Gewichtsteile Äther werden in die Grignardverbindung übergeführt, und hierzu wird eine Lösung von 36 Gewichtsteilen α-Phenyl-α-thiazolyl-(2)-γ-dimethylaminobuttersäurenitril in 150 Gewichtsteile Benzol getropft, wobei der Äther abdestilliert. Man erwärmt das Umsetzungsgemisch für 2 Stunden auf 70 bis 80°, kühlt und läßt es in 5 n-Salzsäure einfließen, schüttelt mit Äther aus und macht es alkalisch. Das ausgeschiedene Öl, das 1-Phenyl-1-thiazolyl-(2')-3-dimethylaminopropan, geht bei der Destillation unter 0,3 mm bei 128 bis 132° über.

Beispiel 3

Phenylchinolylacetonitril, bereitet aus Benzylcyanid, 4-Chlorchinolin und Natriumamid, wird mit Natriumamid und Piperidinoäthylchlorid umgesetzt. Das Umsetzungsprodukt wird in Benzol aufgenommen, der benzolische Auszug mit verdünnter Essigsäure ausgeschüttelt, die essigsaure Lösung klar filtriert und mit Natronlauge alkalisch gemacht. Die abgeschiedene Base wird mit Äther aufgenommen, getrocknet und der Äther abdestilliert. Der Rückstand wird mit wenig Petroläther versetzt, wobei sehr bald Kristallisation erfolgt. Das Phenylchinolylpiperidinoäthylacetonitril zeigt den F. = 96 bis 97°.

40 g Phenylchinolylpiperidinoäthylacetonitril werden mit 200 g 70%iger Schwefelsäure etwa 20 Stunden auf 150° erhitzt. Dann wird auf Eis gegossen, mit Natronlauge alkalisch gestellt, ausgeäthert, getrocknet und der Äther abdestilliert. Der Rückstand von 42,5 g erstarrt kristallinisch. Nach dem Umlösen aus Methylalkohol + Wasser schmilzt das 1-Phenyl-1-chinolyl-(4')-3-piperidinopropan bei 82 bis 83°. Das Chlorhydrat zeigt den F. = 201 bis 202°.

Beispiel 4

In eine Lösung aus 58,3 Gewichtsteilen Phenylpyridyl-(2)-acetonitril und 200 Gewichtsteilen Benzol werden bei 25 bis 35° 13 Gewichtsteile Natriumamid eingetragen. Es wird kurze Zeit auf 60 bis 70° erwärmt. Danach wird gekühlt, und 48,5 Gewichtsteile Piperidinoäthylchlorid (Kp_{12} = 68 bis 70°) werden eingetropft. Beim Erwärmen auf 50 bis 60° tritt die Reaktion ein. Zum Schluß wird noch 1 Stunde auf 80° erwärmt, danach mit Wasser zersetzt und die Benzollösung abgetrennt. Nach kleinem Vorlauf geht das α-Phenyl-α-pyridyl-(2)-γ-(N-piperidino)-buttersäurenitril bei 185 bis 190° unter 0,4 mm in 90 bis 95% Ausbeute als rotes viskoses Öl über.

Bei der üblichen Verseifung mit alkoholischer Alkalilauge oder bei der Einwirkung von Grignardreagens entsteht in sehr guter Ausbeute das 1-Phenyl-1-pyridyl-(2')-3-N-piperidinopropan, ein schwach gefärbtes viskoses Öl vom Siedepunkt 160 bis 164° unter 0,25 mm.

Beispiel 5

38,8 Gewichtsteile Phenylpyridyl-(2)-acetonitril, 8,2 Gewichtsteile Natriumamid, 250 Gewichtsteile Benzol werden wie im Beispiel 1 mit 28 Gewichtsteilen N-β-Chloräthylpyrrolidin umgesetzt. In sehr

guter Ausbeute erhält man das α-Phenyl-α-pyridyl-(2)-γ-N-pyrrolidinobuttersäurenitril vom F. = 82 bis 84°.

48,2 Gewichtsteile dieser Nitrilbase werden mit 28 Gewichtsteilen Ätzkali in 150 Gewichtsteilen Butanol 4 Stunden unter Rückfluß erwärmt. Es wird von der Hauptmenge Butanol abdestilliert, mit Wasser versetzt und die entstandene Base abgetrennt.

In nahezu theoretischer Ausbeute wird das 1-Phenyl-1-pyridyl-(2')-3-N-pyrrolidinopropan vom $Kp_{0,15} = 143$ bis 146° erhalten.

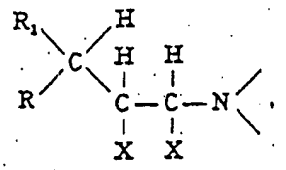
Beispiel 6

40 Gewichtsteile Phenylthiazolyl-(2)-acetonitril werden in Gegenwart von 8,5 Gewichtsteilen Natriumamid und 200 Gewichtsteilen Benzol wie im Beispiel 2 mit 28 Gewichtsteilen N-β-Chloräthyl-pyrrolidin kondensiert. Das α-Phenyl-α-thiazolyl-(2)-γ-N-pyrrolidinobuttersäurenitril entsteht dabei in sehr guter Ausbeute. Es zeigt den F. = 83 bis 85°.

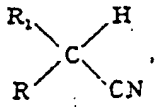
25 Gewichtsteile dieser Base werden mit 10 Gewichtsteilen Ätznatron, 100 Gewichtsteilen Äthanol (90%) 4 Stunden auf dem Dampfbad unter Rückfluß erwärmt. Bei der Aufarbeitung wird in quantitativer Ausbeute das 1-Phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropan vom $Kp_{0,1} = 136$ bis 139° erhalten.

PATENTANSPRUCH:

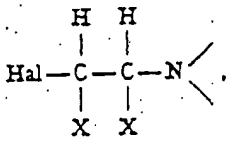
Verfahren zur Herstellung von basischen Verbindungen der allgemeinen Formel



wobei R einen aromatischen, R_1 einen heterocyclischen Rest und X Wasserstoff oder Methyl bedeuten und N ein tertiär gebundenes Stickstoffatom ist, dadurch gekennzeichnet, daß man Nitrile der allgemeinen Formel



wobei R einen aromatischen und R_1 einen heterocyclischen Rest bedeuten, in Gegenwart von halogenwasserstoffabspaltenden Mitteln mit basisch substituierten Halogenalkylen der Formel



in der X Wasserstoff oder Methyl ist, umsetzt und bei den entstandenen Verbindungen nach an sich bekannten Methoden die Cyangruppe unter Ersatz durch ein Wasserstoffatom abspaltet.

[12961/39493]
Translation R Ferber x 6071

Translation of German Patent # 830 193

Inventors: Dr. Gustav Erhart, Dr. Walter Bestian

METHOD FOR PREPARING BASIC COMPOUNDS

It was found that compounds of the general formula

(see original 1)

in which R is an aromatic, and R_1 is a heterocyclic group and X is hydrogen or a methyl group, and N is a tertiary bound nitrogen atom, represent spasmolytics which stand out by their excellent effect on histaminic cramp.

Expediently, these compounds are prepared from nitriles of the general formula

(see original 2)

in which R is an aromatic, and R_1 is a heterocyclic group, on which one allows to react, in the presence of sodium amide or other substances that split off hydrogen halides, a basically substituted halogen alkyl of the formula

(see original 3).

Such halogenides are, for example,

second page begins in original----------

N-β-chloroethyldimethylamine, N-β-chloroethyldiethylamine, 1-chloro-2-dimethylamino propane, N-β-chloroethylpiperidine, N-β-chloroethylpyrrolidine and N-β-chloroethylmorpholine. By the further effect of Grignard reagent, sodium amide and others, the cyano group may be split off while being substituted by a

hydrogen atom. However, one may also treat the cyano group with saponifying means, whereby the intermediarily created carboxilic acids are also converted into the desired compounds while splitting off carbon dioxide.

Example 1

58.2 parts by weight of phenylpyridyl-(2)-acetonitrile having a melting point of 84 to 85°, prepared from benzylcyanide, 2-chloropyridine and sodium amide, are dissolved in 300 parts by weight of toluene, reacted with 13 parts by weight of sodium amide, and subsequently, at 30°, have a solution of 36 parts by weight of β-chloroethyldimethylamine in 50 parts by weight of toluene added. The reaction with this amine takes place at 50 to 60°. The mixture is heated for 2 hours to 100 to 110°, water is added, the toluene solution is extracted using excess acetic acid, and the extract is made alkaline again. The oil thus obtained is fractionally distilled. The α-phenyl-α-pyridyl-(2)-γ-dimethylaminobutyric acid nitrile comes over in almost theoretical yield when distilled under 0.3 mm at 150 to 154°.

To a Grignard solution made up of 43.5 parts by weight of magnesium, 196 parts by weight of ethyl bromide and 400 parts by weight of ether, a solution is allowed to flow in, while simultaneously distilling off the ether, of 205 parts by weight of α-phenyl-α-pyridyl-(2)-γ-dimethylaminobutyric acid nitrile in 400 parts by weight of benzene. The mixture is heated for 1 hour to 80°, then decomposed by water-hydrochloric acid, and the mixture is made alkaline. The oil separating out is the 1-phenyl-1-pyridyl-(2')-3-dimethylaminopropane, which boils under a pressure of 0.3 mm at 130 to 135°. The yield is almost equivalent to the theoretical quantity.

Example 2

49 parts by weight of phenylthiazolyl-(2)-acetonitrile of m.p. 42 to 44°, prepared from benzyl cyanide, 2-chlorothiazole and sodium amide, are heated in 250 parts by weight of benzene with 10.5 parts by weight of sodium amide and 26 parts by weight of β-chloroethyldimethylamine for 1 hour to 50 to 60°, and finally for 2 hours to 80 to 85°, treated with water, and the benzene solution is extracted with acetic acid. The extract is made alkaline and the oil obtained thereby is distilled. The α-phenyl-α-thiazolyl-(2)-γ-dimethylaminobutyric acid nitrile boils under 0.3 mm at 152 to 155°.

9.5 parts by weight of magnesium, 44 parts by weight of ethyl bromide and 150 parts by weight of ether are transferred to the Grignard compound, and into this a solution of 36 parts by weight α-phenyl-α-thiazolyl-(2)-γ-dimethylaminobutyric acid nitrile in 150 parts by weight of benzene is added dropwise, during which the ether distills off. The reaction mixture is heated for 2 hours to 70 to 80°, is cooled and allowed to flow into 5 n hydrochloric acid, is extracted with ether and made alkaline. The separated oil, the 1-phenyl-1-thiazolyl-(2')-3-dimethylaminopropane comes over during distillation under 0.3 mm at 128 to 132°.

Example 3

Phenylquinolylacetonitrile, prepared from benzyl cyanide, 4-chloroquinoline and sodium amide, is reacted with sodium amide and piperidinoethyl chloride. The reaction product is taken up in benzene, the benzene extract is shaken out with diluted acetic acid, the acetic acid solution is filtered clear and made alkaline with sodium hydroxide solution. The separated base is

taken up in ether, is then dried, and the ether is distilled off. The residue has a little petroleum ether added to it and it very soon begins to crystallize. The phenylquinolylpiperidinoethylacetonitrile has a melting point of 96 to 97°.

40 g of phenylquinolylpiperidinoethylacetonitrile are heated with 200 g of 70% sulfuric acid for approximately 20 hours to 150°. The mixture is poured over ice, made alkaline with sodium hydroxide solution, extracted with ether, and the ether is distilled off. The residue of 42.5 g solidifies in crystals. After recrystallization from methyl alcohol and water, the 1-phenyl-1-quinolyl-(4')-3-piperidinopropane melts at 82 to 83°. The chlorohydrate has a melting point of 201 to 202°.

Example 4

Into a solution of 58.3 parts by weight of phenylpyridyl-(2)-acetonitrile and 200 parts by weight benzene, 13 parts by weight of sodium amide are added at 25 to 35°. The mixture is heated for a short time to 60 to 70°. Then it is cooled, and 48.5 parts by weight of piperidinoethyl chloride ($b.p._{12}$ 68 to 70°) are added dropwise. When the mixture is heated to 50 to 60°, a reaction sets in. At the end, heating is continued for 1 hour more to 80°, then decomposed with water, and the benzene solution is separated. After small foreruns, the α-phenyl-α-pyridyl-(2)-γ-(N-piperidino)-butyric acid nitrile comes over at 185 to 190° under 0.4 mm and a 90 to 95% yield as a red viscous oil.

In the case of the usual saponification with alcoholic lye or in the case of the action of Grignard reagent, there is created, in very good yield, 1-phenyl-1-pyridyl-(2')-3-N-piperidinopropane,

a weakly colored viscous oil having a boiling point of 160 to 164^0 under 0.25 mm.

Example 5

38.8 parts by weight phenylpyridyl-(2)-acetonitrile, 8.2 parts by weight sodium amide, 250 parts by weight benzene are reacted, as in Example 1, with 28 parts by weight N-β-chloroethylpyrrolidine. In a very good

third page begins in original----------

yield one obtains the α-phenyl-α-pyridyl-(2)-γ-N-pyrrolidinobutyric acid nitrile, having a melting point of 82 to 84^0.

48.2 parts by weight of this nitrile base are heated with 28 parts by weight of caustic alkali in 150 parts by weight of butanol for 4 hours under reflux. Butanol is distilled off from the main quantity, water is added, and the base created is separated.

1-phenyl-1-pyridyl-(2')-3-N-pyrrolidinopropane having a boiling $point_{0.15}$ of 143 to 146^0 is obtained in an almost theoretical yield.

Example 6

40 parts by weight phenythiazolyl-(2)-acetonitrile are condensed as in Example 2 with 28 parts by weight of N-β-chloroethylpirrolidine, in the presence of 8.5 parts by weight sodium amide and 200 parts by weight benzene. The α-phenyl-α-thiazolyl-(2)-γ-N-pyrrolidinobutyric acid nitrile is created in

this context in a very good yield. It has a melting point of 83 to 85^0.

25 parts by weight of this base are heated with 10 parts by weight of caustic soda, 100 parts by weight of ethanol (90%) on a steam bath under reflux for 4 hours. In quantitative yield, the preparation yields 1-phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropane having a boiling $point_{0.1}$ of 136 to 139^0.

What is claimed is:

1. A method for preparing basic compounds of the general formula

(see original 4)

in which R is an aromatic, and R_1 is a heterocyclic group and X is hydrogen or a methyl group, and N is a tertiary bound nitrogen atom,
wherein one reacts nitriles of the general formula

(see original 5),

in which R is an aromatic, and R_1 is a heterocyclic group, in the presence of means for splitting off hydrogen halides using basically substituted halogen alkyl groups of the formula

(see original 6),

in which the X is hydrogen or a methyl group, and in the compounds created, using methods known per se, splits off the cyano group by substituting it by a hydrogen atom.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 872 233 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
21.10.1998 Bulletin 1998/43

(51) Int. Cl.[6]: **A61K 9/14**, A61K 9/20

(21) Application number: **97201100.1**

(22) Date of filing: **14.04.1997**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV RO SI

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(54) Antiretroviral compositions with improved bioavailability

(57) The present invention is concerned with novel pharmaceutical compositions of loviride which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms have a high drug content and can be administered at any time of the day independently of the food taken in by said patient. These novel compositions comprise particles obtainable by melt-extruding a mixture comprising loviride and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

EP 0 872 233 A1

Printed by Xerox (UK) Business Services
2.16.3/3.4

Description

The present invention is concerned with novel pharmaceutical compositions of loviride which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms have a high drug content and can be administered at any time of the day independently of the food taken in by said patient. These novel compositions comprise particles obtainable by melt-extruding a mixture comprising loviride and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

The development of pharmaceutical compositions having good bioavailability of loviride, a compound that is practically insoluble in aqueous media, remains one of the main challenges of pharmaceutical development of this compound.

The term "practically insoluble" or "insoluble" is to be understood as defined in the United States Pharmacopeia, i.e. a "very slightly soluble" compound requiring from 1000 to 10,000 parts of solvent for 1 part of solute; a "practically insoluble" or "insoluble" compound requiring more than 10,000 parts of solvent for 1 part of solute. The solvent referred to herein is water.

Loviride or (±)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide, is an antiretroviral non-nucleoside reverse transcriptase inhibitor developed for oral, parenteral and topical administration to patients suffering from HIV infection and is disclosed in WO-92/00952 (23.01.1992). Loviride is currently undergoing extensive phase II evaluations as monotherapy and in combinations with other anti-HIV compounds. As its half-life is short, loviride is admininistered three times a day (t.i.d.). Suitable oral doses are 100 mg t.i.d., 200 mg t.i.d. or even 300 mg t.i.d. The oral formulation can be a capsule comprising drug-coated beads. Since not more than 100 mg of the active ingredient can be formulated into one capsule, patients are expected to ingest from 3 to 9 capsules a day. Clearly, a dosage form having a higher drag content, e.g. 200 mg or even 300 mg would mark a significant step forward.

The term "loviride" as used hereinafter is to be interpreted broadly and comprises the free base form and the pharmaceutically acceptable addition salts of loviride, or of one of its enantiomers, or of a mixture of its two enantiomers. The preferred loviride compound is the racemic mixture of the enantiomers in the free base form ; to all practical purposes this compound is insoluble. Its solubility at room temperature in water at a pH of 6.5 is less than 0.1 mg/100ml. The acid addition forms may be obtained by reaction of the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-butenedioic, (E)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

In order to achieve the desired antiretroviral effect, it is essential that therapeutically effective plasma levels of loviride can be maintained. As loviride is practically insoluble, effective formulations should be designed in such a manner that the drug is readily bioavailable. In other words, the main problem with the administration of loviride in therapeutically effective amounts is concerned with ensuring that a sufficient amount of loviride remains in a bioavailable physical form (solution, microcrystal) sufficiently long to allow it to get into the circulation, and does not convert into a form that is not readily bioavailable, in particular crystalline loviride (which is formed for example when loviride precipitates in an aqueous medium). To that purpose loviride in capsules is preferably ingested during or at the end of a meal. This, however, limits the ease with which the patients can comply with their prescribed therapy ; for example, some patients are not able to eat normally or swallow medicaments easily (let alone three times a day) because of illness, nausea or because of opportunistic infections of the esophagus. It would therefore be highly desirable to have pharmaceutical dosage forms which have a high drug content and can be administered to a patient at any time of the day independently of food taken in. i.e. dosage forms which can be administered to patients in a fasted state.

The present invention provides pharmaceutical compositions of loviride and a water-soluble polymer which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms can be administered at any time of the day independently of the food taken in by said patient. The bioavailability of the drug from these dosage forms in fasted and in fed patients is comparable. The dosage forms can be prepared easily, for example by conventional tabletting techniques. The dosage forms comprise a therapeutically effective amount of novel particles as described in detail hereunder.

Said novel particles consist of a solid dispersion comprising

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers; and
(b) one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or

components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called "a solid solution" hereinafter. Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline solid phase.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to particles having domains or small regions wherein amorphous or microcrystalline (a), or amorphous or microcrystalline (b), or both, are dispersed more or less evenly in another phase comprising (b), or (a), or a solid solution comprising (a) and (b). Said domains are regions within the particles distinctively marked by some physical feature, small in size compared to the size of the particle as a whole, and evenly and randomly distributed throughout the particle. Microcrystalline (a) typically has a domain size of up to about 25 μm, preferably up to 20 μm.

The particles according to the present invention can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

The melt-extrusion process comprises the following steps :

a) mixing the components (a) and (b),
b) optionally blending additives with the thus obtained mixture,
c) heating the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

The terms "melt" and "melting" should be interpreted broadly. For our purposes, these terms not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less evenly into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

One of the most important parameters of melt extrusion is the temperature at which the melt-extruder is operating. It was found that the operating temperature can easily range between about 120°C and about 300°C. At temperatures lower than 120°C, loviride will not dissolve sufficiently in most water-soluble polymers and the extrudate will not have the required bioavailability. In addition, the process is difficult because of the high viscosity of the mixture. At temperatures of more than 300°C the water-soluble polymer may decompose to an unacceptable level. It may be noted that there is no need to fear decomposition of loviride at temperatures up to 300°C, since this active ingredient is thermally very stable.

The throughput rate is also of importance because even at relatively low temperatures the water-soluble polymer may start to decompose when it remains too long in contact with the heating element.

It will be appreciated that the person skilled in the art will be able to optimize the parameters of the melt extrusion process within the above given ranges. The working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Most of the energy needed to melt, mix and dissolve the components in the extruder can be provided by the heating elements. However, the friction of the material within the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogenous melt of the components.

Spray-drying of a solution of the components also yields a solid dispersion of said components and may be a useful alternative to the melt-extrusion process, particularly in those cases where the water-soluble polymer is not sufficiently stable to withstand the extrusion conditions and where residual solvent can effectively be removed from the solid dispersion. Yet another possibility consists of preparing a solution of the components, pouring said solution onto a large surface, and evaporating the solvent therefrom.

The solid dispersion product is milled or ground to particles having a particle size of less than 600 μm, preferably less than 400 μm and most preferably less than 125 μm. The particle size proves to be an important factor determining the speed with which tablets having sufficient hardness can be manufactured on a large scale. The particle size distribution is such that more than 70% of the particles (measured by weight) have a diameter ranging from about 50 μm to about 500 μm, in particular from about 50 μm to about 200 μm and most in particular from about 50 μm to about 125 μm. Particles of the dimensions mentioned herein can be obtained by sieving them through nominal standard test

sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Preferred are particles wherein the loviride is in a non-crystalline phase as these have an intrinsically faster dissolution rate than those wherein part or all of the loviride is in a microcrystalline form.

Preferably, the solid dispersion is in the form of a solid solution comprising (a) and (b). Alternatively, it may be in the form of a dispersion wherein microcrystalline (a) is dispersed more or less evenly in a solid solution comprising (a) and (b).

The water-soluble polymer in the particles according to the present invention is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

The molecular weight of the HPMC normally affects both the release profile of the milled extrudate as well as its physical properties. A desired release profile can thus be designed by choosing an HPMC of an appropriate molecular weight ; for immediate release of the active ingredient from the particles, a low molecular weight polymer is preferred. High molecular weight HPMC is more likely to yield a sustained release pharmaceutical dosage form. The molecular weight of a water-soluble cellulose ether is generally expressed in terms of the apparent viscosity at 20°C of an aqueous solution containing two percent by weight of said polymer. Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s, because this yields particles from which superior oral dosage forms of loviride can be prepared as will be discussed hereunder and in the experimental part.

The weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 8, preferably 1 : 1 to 1 : 5. In the case of (loviride) : (HPMC 2910 5 mPa.s), said ratio may range from about 1 : 1 to about 1 : 2, and optimally is about 1 : 1.5 (or 2 : 3). The weight by weight ratio of loviride to other water-soluble polymers may be determined by a person skilled in the art

by straightforward experimentation. The lower limit is determined by practical considerations. Indeed, given the therapeutically effective amount of loviride (from about 100 mg to about 300 mg, preferably about 200 mg per administration), the lower limit of the ratio is determined by the maximum amount of mixture that can be processed into one dosage form of practical size. When the relative amount of water-soluble polymer is too high, the absolute amount of mixture needed to reach the therapeutic level will be too high to be processed into one capsule or tablet. Tablets, for example, have a maximum weight of about 1 g, and the extrudate can account for maximally about 90 % (w/w) thereof. Consequently, the lower limit of the amount of loviride over hydroxypropyl methyl cellulose will be about 1 : 8 (100 mg loviride + 800 mg water-soluble polymer).

On the other hand, if the ratio is too high, this means the amount of loviride is relatively high compared to the amount of water-soluble polymer, then there is the risk that the loviride will not dissolve sufficiently in the water-soluble polymer, and thus the required bioavailability will not be obtained. The degree to which a compound has dissolved into a water-soluble polymer can often be checked visually : if the extrudate is clear then it is very likely that the compound will have dissolved completely in the water-soluble polymer. The 1 : 1 upper limit is determined by the fact that above said ratio it was observed that the extrudate resulting from extruding loviride with HPMC 2910 5 mPa.s is not "clear", presumably due to the fact that not all of the loviride has dissolved in the HPMC. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular water-soluble polymers. Since this can be established easily but for the experimentation time involved, solid dispersions wherein the ratio (a) : (b) is larger than 1 : 1 are also meant to be comprised within the scope of the present invention.

Preferred particles are those obtainable by melt-extrusion of the components and grinding, and optionally sieving. More in particular, the present invention concerns particles consisting of a solid dispersion comprising two parts by weight of loviride and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extruding the blend at a temperature in the range of 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

The particle as described hereinabove may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Said excipients should not be heat-sensitive, in other words, they should not show any degradation or decomposition at the working temperature of the melt-extruder.

In the current loviride : HPMC 2910 5 mPa.s formulations, the amount of plasticizer is preferably small, in the order of 0 % to 15 % (w/w), preferably less than 5 % (w/w). With other water-soluble polymers though, plasticizers may be employed in much different, often higher amounts because plasticizers as mentioned hereinbelow lower the temperature at which a melt of (a), (b) and plasticizer is formed, and this lowering of the melting point is advantagous where the polymer has limited thermal stability. Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molcular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycollate; and amines such as monoethanolamine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

Once the extrudate is obtained, it is milled and sieved and used as a "normal" ingredient to make pharmaceutical dosage forms.

The particles of the present invention can be formulated into pharmaceutical dosage forms comprising a therapeutically effective amount of particles. Although, at first instance, pharmaceutical dosage forms for oral administration such as tablets and capsules are envisaged, the particles of the present invention can also be used to prepare pharmaceutical dosage forms e.g. for rectal administration. Preferred dosage forms are those adapted for oral administration shaped as a tablet. They can be produced by conventional tabletting techniques with conventional ingredients or excipients and with conventional tabletting machines. In addition, they can be produced at substantially lower cost than coated cores. As mentioned above, an effective antiretroviral daily dose of loviride ranges from about 100 mg t.i.d. to about 300 mg t.i.d., and preferably is about 200 mg t.i.d. When one considers that the weight-by-weight ratio of (a) : (b) is maximally about 1 : 1, then it follows that one dosage form will weigh at least 400 mg. In order to facilitate the swallowing of such a dosage form by a patient, it is advantageous to give the dosage form, in particular tablets, an appropriate shape. Tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape. Especially preferred are biconvex oblate tablets. As discussed hereunder in more detail, a film coat on the tablet further contributes to the ease with which it can be swallowed.

Tablets that give an immediate release of loviride upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the particles which are liberated thereby are kept away from one another so that they do not coalesce and do not produce high local

concentrations of loviride with the concommittant danger that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said particles homogeneously throughout a mixture of a disintegrant and a diluent.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose. The amount of disintegrant in immediate release tablets according to the present invention conveniently may range from about 3 to about 15 % (w/w) and preferably is about 7 to 9 % (w/w). This amount tends to be larger than usual in order to ensure that the particles are spread over a large volume of the stomach contents upon ingestion. Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. micro-crystalline cellulose Avicel™), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof. Preferred is a commercial spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially available as Microcelac™.

The tablet may include a variety of one or more other conventional excipients such as binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes.

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, talc, mixtures thereof, and others known in the art. Interesting lubricants and glidants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica. A preferred lubricant is hydrogenated vegetable oil type I, most preferably hydrogenated, deodorized Cottonseed oil (commercially available from Karlshamns as Akofine NF™ (formerly called Sterotex™)). Lubricants and glidants generally comprise 0.2 to 7.0 % of the total tablet weight.

Other excipients such as coloring agents and pigments may also be added to the tablets of the present invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the tablet of the present invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon , orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth, The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylatemethacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain tale as an anti-adhesive. In immediate release tablets according to the invention, the film coat is small and in terms of weight accounts for about 3 % (w/w) of the total tablet weight.

Preferred dosage forms are those wherein the weight of the particles is at least 40 % of the total weight of the total dosage form, that of the diluent ranges from 20 to 40 %, and that of the disintegrant ranges from 3 to 10 %, the remainder being accounted for by one or more of the excipients described hereinabove. As an example of an oral dosage form comprising 200 mg of loviride, the following formula may be given :

loviride (200 mg)
HPMC 2910 5 mPa.s (300 mg)
spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) (282.4 mg)
crospolyvidone (78.4 mg)
talc (25.8 mg)
hydrogenated vegetable oil Type I (8.6 mg)
colloidal anhydrous silica (2.6 mg)
magnesium stearate (2.2 mg), yielding
a tablet core (900 mg), and

HPMC 2910 5 mPa.s (16 mg)
propyleneglycol (4 mg)
talc (3.2 mg)
titanium dioxide (4.8 mg), yielding
a film-coat (28 mg).

Preferred dosage forms according to the present invention are those from which at least 85 % of the available loviride dissolves within 60 minutes when a dosage form equivalent to 200 mg loviride is tested as set forth in USP test ⟨711⟩ in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml water comprising 0.5 % sodium lauryl sulfate, 37°C with paddles turning at 100 rpm. Tablets complying with the preceding definition can be said to have Q > 85 % (60'). Preferably, tablets according to the present invention will dissolve faster and have Q > 85 % (30').

The present invention further concerns a process of preparing particles as described hereinbefore, characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

The invention also concerns solid dispersions obtained by melt-extrusion of

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

It is another object of the invention to provide a process of preparing a pharmaceutical dosage form as described hereinbefore, characterized by blending a therapeutically effective amount of particles as described hereinbefore, with pharmaceutically acceptable excipients and compressing said blend into tablets.

The invention also relates to particles as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

The present invention also concerns the use of particles as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

The invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of loviride as described hereinbefore, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

It has been observed that the tablets of the present invention showed a remarkably lower food-effect than loviride capsules. This means that the difference between taking the medication after a meal or in fasted state is significantly less when the tablet of the present invention is administered than when loviride capsules are administered. This is of course a huge advantage because the medication can be taken in at any time during the day and is no longer dependent upon the intake of a meal. Moreover, patients, who are feeling nauseous or who are not able to eat can still take the tablets of the present invention.

Example 1

a) melt extrusion process

A 40/60 (w/w) mixture of loviride (0.5 kg) and HPMC 2910 5 mPa.s (0.75 kg) were both sieved and mixed in a planetary mixer until the mixture was homogenous.

The mixture was fed into a twin screw melt extruder of the type APV-Baker MP19 L/D 15 having the following operating parameters : temperature of the first compartment was 225°C, temperature of the second compartment was 235°C, the twin screw had a rate of 250 revolutions/min and was extruded at a fedd rate of 1.5 kg/h. The extrudate was brought in a hammer mill of type Fitzmill, the mesh of the sieve was 0.125 inch (= 0.32 cm) and revolving speed was 1640 revolutions per minute. The milled extrudate was again brought in a hammer mill, this time with a sieve of mesh 0.063 inch (= 0.16 cm) and a revolving speed of 1640 revolutions per minute. Yield was 1.03 kg (82.4 %).

b) preparation of a tabletting mixture

Microcrystalline cellulose (90.2 g, 24.4 % (w/w)), Crospovidone (25 g, 6.8 % (w/w)), Aerosil (colloidal silicon dioxide) (1.1 g, 0.3 % (w/w)) and Sterotex (3.7 g, 1 % (w/w)) were sieved (mesh width of 850 μm) and mixed together with the milled extrudate (250 g, 67.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes).

c) Tabletting

Using the mixture obtained in b) round biconvex tablets of 370 mg (die diameter = 10 mm, radius of curvature = 15 mm) were prepared on a Korsch II operating at a speed of 10,000 tablets/hour, a compression pressure of 1500 to 1950 kg /cm^2 (147 - 191.1 MPa). The uncoated tablets had a disintegration time of less than 1 minute in neutral water and hardness = 6.23 daN. The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and tale (8 g) in water (400 g) according to art-known procedures.

Example 2

The process as described in example 1 was repeated, but the blending and tabletting steps were carried out as follows :

Microcelac (141.2 g, 31.4 % (w/w)), Crospovidone (39.2 g, 8.7 % (w/w)) and Aerosil (colloidal silicon dioxide) (1.3 g, 0.3 % (w/w)) were sieved (mesh width of 850 µm) and mixed together with the milled extrudate (250 g, 55.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes). Then there was added tale (12.9 g, 2.9 % (w/w)), magnesium stearate (1.1 g, 0.24 % (w/w)) and Sterotex (4.3 g, 1 % (w/w)) and the whole was mixed for another 5 minutes. The blend was tabletted on a Korsch II to round bieonvex tablets of 450 mg (die diameter 11.5 mm, radius of curvature = 15 mm). The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and talc (8 g) in water (400 g) according to art-known procedures.

Example 3

The process as described in example 1 was repeated, but the blending and tabletting steps were carried out as follows :

Microcelac (282.4 g, 31.4 % (w/w)), Crospovidone (78.4 g, 8.7 % (w/w)) and Aerosil (colloidal silicon dioxide) (2.6 g, 0.3 % (w/w)) were sieved (mesh width of 850 µm) and mixed together with the milled extrudate (500 g, 55.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes). Then there was added tale (25.8 g, 2.9 % (w/w)), magnesium stearate (2.2 g, 0.24 % (w/w)) and Sterotex (8.6 g, 1 % (w/w)) and the whole was mixed for another 5 minutes. The blend was tabletted on a Excenterpress Courtoy 27 to oblate biconvex tablets of 900 mg. The length of the die was 19 mm, breadth 9.5 mm, and the radius of curvature 9.57 mm. The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and talc (8 g) in water (400 g) according to art-known procedures.

Example 4 : Dissolution Properties

In-vitro dissolutions studies were performed on the 100 mg tablet formulation of Example 1. The medium was 900 ml water comprising 0.5 % sodium lauryl sulfate at 37°C in Apparatus 2 (USP 23, ⟨711⟩ Dissolution, pp. 1791-1793) (paddle, 100 rpm). The concentration of the active ingredient loviride dissolved in the test medium was determined by removing a 3 ml sample at the indicated time, measuring its absorbance at 266 nm and calculating the concentration therefrom.

The following results were obtained :

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	84.1	66.3	82.3	83.7	80.5	82.4	79.9
30	100.4	96	100.0	101.5	97.4	97.1	98.8
45	102.6	102.6	103.1	103.9	100.0	99.8	102.0
60	102.1	102.3	103.0	103.3	99.8	99.7	101.7
90	102.9	103.6	104.0	104.1	100.7	99.9	102.5

Example 5 : Pharmacokinetic properties

In this study 12 healthy volunteers in fasting conditions were administered a tablet of example 1 (100 mg loviride). Plasma levels of each of the loviride enantiomers were determined and the following bioavailability data were calculated therefrom.

(-)-loviride : C_{max} = 155 ± 66 ng/ml
AUC_{last} = 1,347 ± 512 ng.h/ml

(+)-loviride : C_{max} = 890 ± 292 ng/ml
AUC_{last} = 18,180 ± 7,197 ng.h/ml

Claims

1. A particle consisting of a solid dispersion comprising

   (a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
   (b) one or more pharmaceutically acceptable water-soluble polymers.

2. A particle according to claim 1 having a particle size of less than 600 μm.

3. A particle according to claim 1 or 2 wherein the loviride is in a non-crystalline phase.

4. A particle according to claim 3 wherein the solid dispersion is in the form of a solid solution comprising (a) and (b), or in the form of a dispersion wherein amorphous or microcrystalline (a), or amorphous or microcrystalline (b), or both, are dispersed more or less evenly in another phase of (b), or of (a), or in a solid solution comprising (a) and (b).

5. A particle according to the preceding claims wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

6. A particle according to claim 5 wherein the water-soluble polymer is selected from the group comprising

   - alkylcelluloses such as methylcellulose,
   - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
   - hydroxypropylcellulose and hydroxybutylcellulose,
   - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
   - carboxyalkylcelluloses such as carboxymethylcellulose,
   - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
   - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
   - carboxyalkylcellulose esters,
   - starches,
   - pectines such as sodium carboxymethylamylopectine,
   - chitine derivates such as chitosan,
   - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
   - polyacrylic acids and the salts thereof,
   - polymethacrylic acids and the salts thereof, methacrylate copolymers,
   - polyvinylalcohol,
   - polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
   - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

7. A particle according to claim 6 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

8. A particle according to claim 7 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 8.

9. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.

10. A particle according to any one of the previous claims consisting of a solid dispersion comprising two parts by weight of loviride and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extrading the blend at a temperature in the range of 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

11. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.

12. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.

13. A dosage form according to claim 12 adapted for oral administration shaped as a tablet.

14. A dosage form according to claim 12 for immediate release of loviride upon oral ingestion wherein said particles are homogeneously distributed throughout a mixture of a diluent and a disintegrant.

15. A dosage form according to claim 13 or 14 surrounded by a film-coat comprising a film-forming polymer, a plasticizer and optionally a pigment.

16. A dosage form according to claim 14 wherein the diluent is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75 : 25), and the disintegrant is crospovidone or croscarmellose.

17. A dosage form according to any one of claims 12 to 16 wherein the weight of said particles is at least 40 % of the total weight of the dosage form.

18. A dosage form according to claim 12 comprising by weight based on the total weight of the dosage form :

loviride (200 mg)
HPMC 2910 5 mPa.s (300 mg)
spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) (282.4 mg)
crospolyvidone (78.4 mg)
talc (25.8 mg)
hydrogenated vegetable oil Type I (8.6 mg)
colloidal anhydrous silica (2.6 mg)
magnesium stearate (2.2 mg), yielding
a tablet core (900 mg), and
HPMC 2910 5 mPa.s (16 mg)
propyleneglycol (4 mg)
talc (3.2 mg)
titanium dioxide (4.8 mg), yielding
a film-coat (28 mg).

19. A dosage form according to any one of claims 12 to 18 from which at least 85 % of the available loviride dissolves within 60 minutes when a dosage form equivalent to 200 mg loviride is tested as set forth in USP test ⟨711⟩ in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml water comprising 0.5 % sodium lauryl sulfate, 37°C with paddles turning at 100 rpm.

20. A process of preparing particles as claimed in any one of claims 1 to 11 characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

21. A solid dispersion obtained by melt-extrusion of

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

22. A process of preparing a pharmaceutical dosage form as claimed in any one of claims 12 to 19 characterized by blending a therapeutically effective amount of particles as claimed in any one of claims 1 to 11 with pharmaceutically acceptable excipients and compressing said blend into tablets.

23. Particles according to any one of claims 1 to 11 for use in preparing a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

24. Use of particles according to any one of claims 1 to 11 for the preparation of a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

25. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of loviride as claimed in any one of claims 12 to 19, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 1100

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	WO 92 00952 A (JANSSEN) * claims * * page 19, line 23 - page 20, line 17 *	1-25	A61K9/14 A61K9/20
A	WO 94 18963 A (JANSSEN) * the whole document *	1-25	
A	WO 96 00068 A (MERCK) * the whole document *	1-25	
A	WO 96 01110 A (JANSSEN) * the whole document *	1-25	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	5 September 1997	Scarponi, U

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 948 321 B1

(12) EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung:
22.10.2003 Patentblatt 2003/43

(21) Anmeldenummer: **97953773.5**

(22) Anmeldetag: **10.12.1997**

(51) Int Cl.[7]: **A61K 9/26**, A61K 9/16

(86) Internationale Anmeldenummer:
PCT/EP97/06893

(87) Internationale Veröffentlichungsnummer:
WO 98/025590 (18.06.1998 Gazette 1998/24)

(54) ZUBEREITUNG IN FORM EINES WAHLWEISE WIRKSTOFFHALTIGEN MATRIXMATERIAL-HILFSSTOFF COMPOUNDS

PREPARATION IN FORM OF A MATRIX MATERIAL-AUXILIARY AGENT COMPOUND CONTAINING OPTIONALLY AN ACTIVE SUBSTANCE

PREPARATION SOUS FORME D'UN COMPOSE MATERIAU MATRICIEL-MATIERE AUXILIAIRE RENFERMANT EVENTUELLEMENT UNE MATIERE ACTIVE

(84) Benannte Vertragsstaaten:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Benannte Erstreckungsstaaten:
AL LT LV RO SI

(30) Priorität: **12.12.1996 DE 19651734**
12.11.1997 DE 19749897

(43) Veröffentlichungstag der Anmeldung:
13.10.1999 Patentblatt 1999/41

(73) Patentinhaber: **DDS DRUG DELIVERY SERVICE GESELLSCHAFT ZUR FÖRDERUNG DER FORSCHUNG IN PHARMAZEUTISCHER TECHNOLOGIE UND BIOPHARMAZIE MBH**
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(56) Entgegenhaltungen:
EP-A- 0 192 173
EP-A- 0 682 945
WO-A-94/00111
DE-C- 3 506 276
DE-C- 4 122 591

- **DATABASE WPI Week 9722 Derwent Publications Ltd., London, GB; AN 97-241649 XP002073923 & JP 09 077 669 A (TAKEDA CHEM IND LTD) , 25. März 1997**

Printed by Jouve, 75001 PARIS (FR)

EP 0 948 321 B1

Beschreibung

[0001] Die Erfindung bezieht sich auf eine Zubereitung in Form eines Compounds gemäß Anspruch 1 oder 2, die eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine Phase eines matrixbildenden Materials (im folgenden auch Matrixmaterial genannt) ausgewählt aus Polymer und/oder Lipid, d.h. eine polymere Phase und/oder eine Lipidphase mit wenigstens einem Polymer bzw. Lipid aufweist, und damit auf polymer- und/oder lipidhaltige Retardarzneiformen, Verfahren zu deren Herstellung und deren Verwendung, insbesondere zur Herstellung von Tabletten oder anderen größeren Matrixeinheiten.

[0002] Derartige Compounds sind physikalische Verbindungen von mindestens zwei Ausgangsstoffen und werden insbesondere im pharmazeutischen Bereich eingesetzt.

[0003] Es ist bekannt, zur Erreichung einer kontrollierten, verzögerten oder von physiologischen Parametern unabhängigen Freisetzung von

[0004] Wirkstoffen aus einer Zubereitung, die Ausgangsstoffe derart zu verarbeiten, daß die resultierenden Zubereitungen bzw. die aus diesen Zubereitungen hergestellten Arnzeiformen einen die Freisetzung steuernden Überzug aufweisen (z.B. aus Polymeren wie Polymethacrylate oder organischen Molekülen wie Schellack oder Celluloseacetatphthalat) bzw. alternativ ein aus Polymeren bestehendes Matrixsystem aufweisen.

[0005] Unter Verwendung von Polymeren hergestellte, in der Literatur beschriebene Matrixeinheiten zur kontrollierten Freisetzung sind:

1. Polymerpartikel
(z.B. Pellets, Granulatkörner, Mikropartikel)
2. größere Matrixeinheiten
(z.B. Tabletten, Drageekerne und Implantate).

[0006] Die im folgenden näher beschriebenen Partikel sind dadurch gekennzeichnet, daß der Wirkstoff molekulardispers oder partikulär in der polymeren Phase eingebettet ist.

[0007] Die im folgenden näher beschriebenen größeren Matrixeinheiten müssen in der Regel durch das kostenaufwendige Verfahren der Komprimierung nach vorheriger Granulation hergestellt werden.

Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Polymeren:

[0008] Der die Freisetzung kontrollierende Effekt einer solchen Zubereitung oder Arnzeiform, auch "Controlled Release"-Zubereitung (CR-Zubereitung) genannt, wird einerseits durch die Eigenschaften der polymeren Phase selbst, wie beispielsweise die Benetzbarkeit, die Quellbarkeit oder die Kristallinität, und andererseits durch die Struktur der durch die polymere Phase gebildeten Matrix gesteuert. Diese Matrixstruktur, die homogen oder heterogen ausgebildet sein kann, ist entweder bereits in der Zubereitung selbst vorhanden oder entsteht während der Verarbeitung bei der Zubereitung zur Arzneiform.

[0009] Als die Freisetzung beeinflussende Eigenschaften der polymeren Phase seien hier die Löslichkeitseigenschaften genannt. So sind Polymere bzw. Makromoleküle aufgrund ihrer Unlöslichkeit und/oder Quellbarkeit in wäßrigen Lösungsmitteln geeignet, Wirkstoffe, die in einer Matrix solcher Polymere bzw. Makromoleküle eingebettet sind, durch die Poren der Matrix verzögert freizusetzen. Weiterhin sind Arzneiformen mit Polymerstoffen bekannt, die aufgrund der Löslichkeit der Polymere im Magen- oder Darmsaft eine den Ort der Freisetzung kontrollierende Zubereitung darstellen.

[0010] Bei diesen die Wirkstofffreisetzung kontrollierenden Zubereitungen sind insbesondere zwei Gruppen zu unterscheiden.

[0011] Einerseits sind polymerhaltige Partikel in einer Größenordnung von ca. 0,01 bis 2 mm bekannt, die auch als Mikropartikel (0,05 bis 0,2 mm), Granulatkörner oder Pellets bezeichnet werden. Aber auch die erst seit kürzerer Zeit bekannten Mikropartikel bzw. Mikrosphärulen mit einer typischen Größe von 50 bis 200 µm, Nanopartikel, Nanopellets und Nanosphärulen werden, sofern sie eine polymere Phase aufweisen, der Gruppe der polymerhaltigen Partikel zugeordnet. Die Partikel liegen als eigenständige Freisetzungseinheit in Form einer partikulären Matrix vor, wobei dann bereits die Zubereitung eine Matrixstruktur aufweist.

[0012] Andererseits können die in der vorliegenden Anmeldung beschriebenen Partikel zu größeren Freisetzungseinheiten bzw. größeren Matrixeinheiten vereinigt werden. Diese Weiterverarbeitung wird weiter unten im einzelnen ausgeführt.

[0013] Als Beispiele der partikulären Matrices, deren Partikel eigenständige Freisetzungseinheiten bilden, seien die Dispersion von Mikropartikeln zur parenteralen Injektion, die eine kontrollierte Freisetzung von LH-RH-Analoga erlauben, sowie die Füllung von Pellets in eine Gelatinekapsel bei Handelspräparaten wie Sympathomimetika genannt. Diese werden von Müller, R.H., Hildebrand G.E. (Hrsg.) in "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997), von Bauer, K.H., Frömming, K-H., Führer, C. in "Pharmazeutische Technologie"; Georg Thieme Verlag Stuttgart, New York, (1991), sowie von List, P.H. "Arzneiformenlehre" Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1986), beschrieben.

[0014] Weiterhin sind in der EP 0 261 677 polymerhaltige Zusammensetzungen beschrieben, die eine verzögerte Freisetzung des Wirkstoffs ermöglichen sollen. Zur Herstellung dieser Zusammensetzungen wird ein Sprühtrocknungsverfahren offenbart, so daß unter Anwendung der Lehre dieser Druckschrift Partikel mit einer

Größe von mindestens 30 µm erhalten werden, die den Wirkstoff in gleichmäßiger Verteilung aufweisen.

[0015] Zur Herstellung solcher Zubereitungen mit partikulärer Matrixstruktur werden in der Literatur mehrere Verfahren beschrieben.

[0016] Bei den Verfahren nach der "solvent evaporation"- oder der "inliquid-drying"-Methode ist das Polymer bzw. der Matrixbildner eine in einem organischen Lösungsmittel lösliche Substanz (z.B. Polymere wie Polylactide, Polylactid/Glycolid). Das Polymer wird in einem organischen Lösungsmittel gelöst, der Wirkstoff wird ebenfalls in der organischen Phase gelöst oder - im Falle unlöslicher Wirkstoffe - dispergiert. Die den Wirkstoff enthaltende Lösung des Polymers bzw. Matrixbildners wird dann in eine wäßrige Tensidlösung gegeben und durch Rühren eine O/W-Emulsion hergestellt. Das organische Lösungsmittel wird dann entfernt und der Matrixbildner präzipitiert. Es entstehen feste Pellets bzw. Mikropartikel. Je nach der Methode zur Entfernung des Lösungsmittels unterscheidet man zwischen der "solvent evaporation"und der "in-liquid-drying"-Methode.

[0017] Diese Verfahren wurden von Speiser, P. in Müller, R.H., Hildebrand, G.E. (Hrsg.) "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart (1997), von Beck, L.R., Pope, V.Z., Cowsar, D.R., Lewis, D.H., Tice, T.R. in "Evulation of a new three-month injectable contraceptive microsphere system in primates (baboons)", Contracept. Deliv.1 Syst., 1, 79-80 (1980), von Beck, L. R., Flowers, C.E., Pope, V.Z., Tice, T.R. Wilborn, W.H. in "Clinical evaluation of an improved injectable microcapsule contraceptive system" in Amer. J. Obstet. Gynecol. 147 (7), 815-821 (1983) und von Beck, L.R., Pope, V.Z., Flowers, C.E., Cowsar, D.R., Tice, T.R., Lewis, D.H., Dunn, R.L., Moore, A.B., Gilley, R.M. in "Poly (d,l-lactide-coglycolide)/norethisterone microcapsules: An injectable biogradable contraceptive" in Biol. Reprod. 28, 186-195 (1983a) beschrieben.

[0018] Mit diesen Verfahren können sehr feine Partikel im Bereich von wenigen Mikrometern erhalten werden. Nachteilig ist jedoch der große Aufwand, mit dem die Herstellungsmethode verbunden ist, sowie die Belastung der Partikel mit Restlösungsmittel. Aus diesem Grund gibt es auch bisher in Deutschland noch kein Produkt, das nach einer dieser Verfahren hergestellt worden ist und die Zulassungskriterien für ein Arzneimittel erfüllt.

[0019] Alternativ kann man die den Wirkstoff enthaltende Lösung des Polymers bzw. des Matrixbildners versprühen. Auch hier ist ein Restgehalt an organischen Lösungsmitteln im Produkt aufgrund des Herstellungsverfahrens nicht zu vermeiden. Nach diesem Verfahren hergestellte Produkte, wie z.B. Mikropartikel zur parenteralen Applikation von Bromocriptin, werden von Fahr, A., Kissel, T. in Müller, R.H., Hildebrand, G.E. (Hrsg.), "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997) beschrieben. Sie sind auf dem pharmazeutischen Markt. Das Problem des Restlösungsmittelgehalts ist jedoch nur dadurch verdrängt worden, daß hier auch die Freisetzung des toxischen Lösungsmittels verzögert und damit in geringer Menge erfolgt. Mit der pro Tag aus der Matrix freigegebenen Menge bleibt man unter dem maximalen täglich tolerierten Wert.

[0020] Alle bisher genannten Verfahren sind dadurch gekennzeichnet, daß die polymere Phase bzw. der Matrixbildner in einer gelösten Form als Molekül vorliegt und sich in einem organischen Lösungsmittel befindet. Es entstehen partikuläre Zubereitungen, deren polymere Phase den Wirkstoff molekulardispers oder in Form feiner Partikel enthält. Diese Zubereitungen weisen eine sogenannte heterogene Matrixstruktur auf, wie auch von Fahr, A., Kissel, T. in Müller, R.H., Hildebrand, G.E. (Hrsg.), "Pharmazeutische Technologie: Moderene Arnzeiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997) beschrieben ist.

[0021] Ein weiteres Verfahren zur Herstellung einer partikulären Zubereitung mit polymerer Phase unter Vermeidung der Verwendung von organischen Lösungsmittel wird in der EP 0 361 677 dargestellt. Der nach dieser Druckschrift wasserlösliche Matrixbildner bzw. die polymere Phase wird in Wasser gelöst (z.B. Ethylacrylat/Methacrylat-Copolymer in ammoniakalischer Lösung), der Wirkstoff wird ebenfalls gelöst oder dispergiert und - im Gegensatz zur "solvent evaporation"- und "in liquid-drying"-Methode - anstatt einer O/W - nun eine W/O-Emulsion hergestellt. Dispersionsmedien sind mit Wasser nicht mischbare organische Lösungsmittel, z.B. flüssiges Paraffin oder Methylenchlorid. Der Matrixbildner kann in Wasser gelöst oder auch in der Wasserphase emulgiert werden. Im zweiten Fall wird eine Emulsion in einem mit Wasser nicht mischbaren organischen Lösungsmittel dispergiert. Durch aufwendige azeotrope Destillation von Wasser und organischem Lösungsmittel werden Polymerpartikel ausgefällt, die den Wirkstoff in molekulardisperser oder partikulärer Verteilung einschließen. Die Gewinnung der Partikel erfolgt durch Separation mittels Filtration und anschließendes Waschen.

[0022] In der US-A-5 043 280 wird ein Verfahren zur Herstellung einer partikulären Zubereitung durch Extraktion in überkritischen Gasen beschrieben. Hierbei ist der Matrixbildner - wie bei der "solvent evaporation" - eine in einem organischen Lösungsmittel lösliche Substanz, wie z.B. ein Polymer. Das Polymer wird in einem organischen Lösungsmittel gelöst, und der Wirkstoff wird ebenfalls gelöst oder - im Falle unlöslicher Wirkstoffe - in der organischen Phase dispergiert. Die den Wirkstoff enthaltende Lösung des Matrixbildners wird dann in einer überkritischen Gasphase fein versprüht. Feine Tropfen verteilen sich im überkritischen Gas, das das organische Lösungsmittel aus den Tropfen extrahiert. Als Folge kommt es zur Präzipitation von Partikeln, die den Wirkstoff enthalten.

[0023] Auch diese genannten Verfahren führen zu Zu-

bereitungen, die den Wirkstoff in molekulardisperser bzw. partikulärer Form in der polymeren Phase eingebettet aufweisen. Durch diesen verfahrensbedingten Einschluß des Wirkstoffs in die polymere Phase weist die Außenphase der Zubereitung größtenteils Polymer auf, wodurch auch die pharmazeutischen Eigenschaften, die für eine eventuelle Weiterverarbeitung von Bedeutung sind, festgelegt werden. Ferner weisen die genannten Zubereitungen den Nachteil auf, daß sie nur unter erheblichem Kosten- und Zeitaufwand herstellbar sind.

[0024] DE-A-35 06 276 offenbart ein Verfahren zur Herstellung von Direkttablettiermitteln, wobei Cellulosepulver mit einer heißen Lösung von 50%-iger Lactose in Wasser vermischt und die so erhaltene Mischung abgekühlt wird. Die so erhaltene Masse wird anschließend granniiert und getrocknet. Alternativ kann eine Mischung von mikrokristalliner Lactose mit Cellulose pulver in kattern Wasser aufgeschlämmt und anschließend sprühgetrocknet werden.

[0025] Die Möglichkeit der Weiterverarbeitung partikulärer, polymerhaltiger Zubereitungen zu Arzneiformen, die größere Matrixeinheiten aufweisen, wie beispielsweise zu Tabletten, Drageekernen oder Implantaten ist bekannt. So wird von Müller, R.H., Hildebrand, G. E. (Hrsg.) in Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997), die Herstellung von LH-RH-Analoga enthaltenden Implantaten beschrieben. Von besonderer Bedeutung ist dabei die Herstellung von Tabletten, da diese Arzneiform viele Vorteile aufweist, wie beispielsweise die Möglichkeit zur Verarbeitung fast aller festen Wirkstoffe, die hohe Dosierungsgenauigkeit, die einfache Einnahme und Handhabung und die gute Lager- und Transportfähigkeit.

[0026] Die Herstellung von Arzneiformen, die größere Matrixeinheiten darstellen, und insbesondere von Tabletten, erfolgt üblicherweise durch Komprimierung. Dabei sind zur Verarbeitung der herkömmlichen polymerhaltigen Zubereitungen in Form der partikulären Matrices mehrere Verfahrensschritte notwendig.

[0027] Zuerst werden die verschiedenen Inhaltsstoffe, wie beispielsweise verschiedene Wirkstoffe, Hilfsstoffe und Polymere homogen vermischt. Anschließend wird die Mischung einer Feuchtgranulation durch Zusatz von Binde-, Kleb- oder Lösungsmitteln unterzogen. Das resultierende Granulat wird zum Entzug der Restfeuchte getrocknet. Die Komprimierung zu Tabletten, Drageekernen oder Implantaten erfolgt dann mit dem trockenen Granulat unter Zusatz von weiteren Hilfsstoffen, wie Fließregulierungs-, Schmier- und Formtrennmitteln.

[0028] Nachteilig ist, daß der Wirkstoff während der Feuchtgranulation über lange Zeit der Feuchtigkeit des Binde-, Kleb- oder Lösungsmittels ausgesetzt wird und während des notwendigen Trocknungsverfahrens zwingend einer erhöhten Temperatur ausgesetzt wird. Weiterhin ist das Verfahren aufgrund der verschiedenen Einzelschritte und hierbei benötigter Vorrichtungen und Geräte mit relativ großem Zeitaufwand verbunden und somit kostenintensiv.

[0029] Die Direkttablettierung von Zubereitungen mit polymeren Bestandteilen, die zur Herstellung von Tabletten ohne polymere Phase aufgrund der niedrigen Kosten und der schnellen Durchführbarkeit bereits häufig angewendet wird, ist bisher aufgrund folgender Schwierigkeiten nicht möglich gewesen.

[0030] Zum einen weisen die Polymere durch überwiegend elastische Verformung ein schlechtes Komprimierverhalten auf, da eine Komprimierung üblicherweise hauptsächlich durch plastische Verformung erreicht wird.

[0031] Zum anderen neigt die Tablettiermischung zu einer unerwünschten Entmischung zwischen pulverisierten Wirkstoffen und/oder Hilfsstoffen und Polymeren aufgrund der unterschiedlichen Oberflächenbeschaffenheit und der daraus resultierenden unterschiedlichen Fließeigenschaften. Bei der Direkttablettierung würden daher durch die fortschreitende Entmischung des Tablettierguts stark inhomogene Tabletten erhalten werden.

[0032] Ein weiteres Problem ist das allgemein schlechte Fließverhalten der Polymere. Dies hat zur Folge, daß ein zufriedenstellender Retardeffekt durch die begrenzte Beimischungsfähigkeit von Polymeren zur Tablettiermischung nicht erreicht wird. In der Literatur wird von McGinity, J.W., Cameron, C.G., Cuff. G.W. in "Controlled-release teophylline tablet formulations containing acrylic resins. I. Dissolution properties of tablets", Drug Development and Industrial Pharmacy, 9 (162), 57-68 (1983) und von Cameron, C.G., McGinity, J.W. in "Controlled-release teophylline tablet formulations containing acrylic resins. II. Combination resin formulations" und "III. Influence of filler excipient"., a.a.O. 13(8), 1409-1427 (1987), a.a.O. 13(2), 303-318 (1987) bei Acrylatpolymeren ein in der Regel maximaler Zusatz von 10 - 15% Polymer in einer Tablettenrezeptur zur Direkttablettierung beschrieben.

[0033] Es sind aber auch Retardarzneiformen bekannt, in denen Lipide verwendet werden. Bei solchen in der Literatur beschriebenen Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Lipiden handelt es sich im wesentlichen um:

1. Suppositorien
2. Vaginalglobuli
3. Pellets zur peroralen Applikation (z.B. Mucosolvan retard).

[0034] Im Vergleich zu Polymeren bieten Lipide folgende Vorteile:

1. gute Verträglichkeit in vivo, insbesondere wenn sie aus physiologischen Fettsäuren aufgebaut sind
2. keine toxikologisch bedenklichen Rückstände aus der Produktion (z.B. Katalysatorrückstände)

3. Steuerung der Abbaugeschwindigkeit über chemische Struktur der Lipide
4. kostengünstig

[0035] Somit sind sie neben Polymeren zur Herstellung von CR-Formulierungen einsetzbare Hilfsstoffe.

Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Lipiden - Zubereitungen aus Compounds:

[0036] Die Herstellung von Suppositorien und Vaginalglobuli erfolgt in der Regel durch Ausgießen der arzneistoffhaltigen Mischung (P.H. List, Arzneiformenlehre, Wissenschaftliche Verlagsgesellschaft 1976).

[0037] Die Herstellung von Suppositorien ist auch durch Komprimieren einer Mischung von Lipidpartikeln und Arzneistoffpulver möglich, eine großtechnische Herstellung bereitet jedoch aufgrund der in der Regel schlechten Fließfähigkeit dieser Mischungen beim Abfüllen in die Preßformen Schwierigkeiten. Primär wird diese Methode daher für die Kleinherstellung im Rezepturmaßstab in der Apotheke beschrieben (K. Münzel, J. Büchi, O.-E. Schultz, Galenisches Praktikum, Wissenschaftliche Verlagsgesellschaft Stuttgart, S. 652, 1959). Eingesetzt werden dabei nur Lipide die bei Körpertemperatur schmelzen oder zumindest erweichen.

[0038] Arzneiformen zur peroralen Applikation sind Pellets, die großtechnisch durch Extrusion geschmolzener Lipide mit einem Extrudor und einer Lochscheibe hergestellt werden (Voigt, Lehrbuch der Pharmazeutischen Technologie, Verlag Chemie, 1975). Nachteilig sind hierbei z.B. die Einarbeitung der Arzneistoffe in das Lipid (z.B. durch Dispergieren oder Lösen), die Thermobelastung der Arzneistoffe bei der Extrusion und die Notwendigkeit der Weiterverarbeitung der Pellets in einem zusätzlich Produktionsschritt (z.B. Einfüllung in Hartgelatinekapseln).

[0039] Die Aufgabe der vorliegenden Erfindung liegt nun darin, eine Zubereitung in Form eines matrixmaterialhaltigen Compounds als Retardarzneizubereitungen zu Verfügung zu stellen, die eine Hilfsstoff- und/oder eine Wirkstoffphase und eine Matrixmaterialphase aufweist. Die Zubereitung soll einen ausreichend großen Matrixmaterialanteil aufweisen, so daß eine kontrollierte Freisetzung des enthaltenen oder bei einer Verarbeitung zu größeren Matrixeinheiten nachträglich hinzugefügten Wirkstoffs ermöglicht wird. Außerdem soll die Zubereitung mittels Direkttablettierung zu größeren Matrixeinheiten verarbeitet werden können. Ferner soll ein Verfahren zur Herstellung dieser Zubereitung bzw. Compounds angegeben werden.

[0040] Die erfindungsgemäße Aufgabe wird durch eine matrixmaterialhaltige Retardarzneiform gelöst, die in Form eines Matrixmaterial-Hilfsstoff-Compounds, Matrixmaterial-Wirkstoff-Compounds und/oder Matrixmaterial-Hilfsstoff-Wirkstoff-Compounds vorliegen, wobei das Matrixmaterial ausgewählt ist aus Polymeren und Lipiden, so daß der Compound eine polymere Phase und/oder Lipidphase und eine Hilfsstoff- und/oder eine Wirkstoffphase aufweist.

[0041] Ein solcher Compound kann durch Direktkomprimierung in seine endgültige Arzneimittelform überführt werden.

[0042] Die Erfindung bezieht sich somit auf polymer- oder lipidhaltige Zubereitungen, die

- in Form eines Compounds vorliegen, der eine polymere bzw. lipide Phase mit wenigstens einem Polymer bzw. Lipid, eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff aufweist.

[0043] Erfindungsgemäß ist erkannt worden, daß die Lösung der Aufgabe durch die in Anspruch 1 beschriebene Zubereitung möglich ist, die

a) eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine polymere Phase mit wenigstens einem Polymer aufweist, wobei die polymere Phase inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist, oder

b) eine Lipidphase mit wenigstens einem Lipid, eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff aufweist, wobei die Lipid-phase inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist.

[0044] Insbesondere kann die Polymerphase bzw. die Lipidphase Hilfsund/oder Wirkstoff enthält oder frei davon sein.

[0045] Bei der erfindungsgemäßen Zubereitung kann der Anteil an polymerphase bzw. Lipidphase bezogen auf die Gesamtmenge von Hilfsstoff- und/oder Wirkstoffphase und Polymerphase bzw. Lipidphase zwischen 1 und 98% betragen.

[0046] Insbesondere kann die Zubereitung einen Anteil an Polymer-/Lipidphase von 10 bis 95% aufweisen.

[0047] Ferner kann der Anteil der Polymer-/Lipidphase in der Zubereitung mehr als 15% und höchstens 90% betragen.

[0048] Besonders vorteilhaft zur Ausführung der vorliegenden Erfindung ist es aber, wenn die Polymer-/Lipidphase einen Anteil von 40 bis 70% bezogen auf die Gesamtmenge von Hilfsstoff- und/oder Wirkstoffphase und Polymer-/Lipidphase aufweist.

[0049] Die erfindungsgemäße Zubereitung kann grundsätzlich jede Art von Wirkstoff aufweisen oder frei von Wirkstoff sein. Ferner kann der Wirkstoff der Zubereitung nachträglich, z.B. vor einer Weiterverarbeitung zu größeren Matrixeinheiten zugesetzt werden. Im allgemeinen kann die Zubereitung folgende Wirkstoffgruppen enthalten:

- hydroxylierte Kohlenwasserstoffe
- Carbonylverbindungen wie Ketone (z.B. Haloperidol), Monosaccharide, Disaccharide und Aminozucker
- Carbonsäuren wie aliphatische Carbonsäuren, Ester aliphatischer und aromatischer Carbonsäuren, basisch substituierte Ester aliphatischer und aromatischer Carbonsäuren (z.B. Atropin, Scopolamin), Lactone (z.B. Erythromycin), Amide und Imide aliphatischer Carbonsäuren, Aminosäuren, aliphatische Aminocarbonsäuren, Peptide (z.B. Ciclosporin), Polypeptide, β-Lactamderivate, Penicilline, Cephalosporine, aromatische Carbonsäuren (z. B. Acetylsalicylsäure), Amide aromatischer Carbonsäuren, vinyloge Carbonsäuren und vinyloge Carbonsäureester
- Kohlensäurederivate wie Urethane und Thiourethane, Harnstoff und Harnstoffderivate, Guanidinderivate, Hydantoine, Barbitursäurederivate und Thiobarbitursäurederivate
- Nitroverbindungen wie aromatische Nitroverbindungen und heteroaromatische Nitroverbindungen
- Amine wie aliphatische Amine, Aminoglykoside, Phenylalkylamine, Ephedrinderivate, Hydroxyphenylethanolamine, Adrenalinderivate, Amfetaminderivate, aromatische Amine und Derivate, quartäre Ammoniumverbindungen
- schwefelhaltige Verbindungen wie Thiole und Disulfane, Sulfone, Sulfonsäureester und Sulfonsäureamide
- Polycarbocyclen wie Tetracycline, Steroide mit aromatischem Ring A, Steroide mit alpha,beta-ungesättigter Carbonylfunktion im Ring A und alpha-Ketol-Gruppe (oder Methylketo-Gruppe) am C-17, Steroide mit einem Butenolid-Ring am C-17, Steroide mit einem Pentadienolid-Ring am C-17 und Seco-Steroide
- O-haltige Heterocyclen wie Chromanderivate (z.B. Cromoglicinsäure)
- N-haltige Heterocyclen wie Pyrazolderivate (z.B. Propyphenazon, Phenylbutazon)
- Imidazolderivate (z.B. Histamin, Pilocarpin), Pyridinderivate (z.B. Pyridoxin, Nicotinsäure), Pyrimidinderivate (z.B. Trimetoprim), Indolderivate (z.B. Indometacin), Lysergsäurederivate (z.B. Ergotamin), Yohimbanderivate, Pyrrolidinderivate, Purinderivate (z.B. Allopurinol), Xanthinderivate, 8-Hydroxychinolinderivate, Amino-hydroxy-alkylierte Chinoline, Aminochinoline, Isochinolinderivate (z.B. Morphin, Codein), Chinazolinderivate, Benzopyridazinderivate, Pteridinderivate (z.B. Methotrexat), 1,4-Benzodiazepinderivate, tricyclische N-haltige Heterocyclen, Acridinderivate (z.B. Ethacridin) und Dibenzazepinderivate (z.B. Trimipramin)
- S-haltige Heterocyclen wie Thioxanthenderivate (z. B. Chlorprothixen)
- N,O- und N,S-haltige Heterocyclen wie monocyclische N,0-haltige Heterocyclen, monocyclische N, S-haltige Heterocyclen, Thiadiazinderivate, bicyclische N-S-haltige Heterocyclen, Benzothiadiazinderivate, tricyclische N,S-haltige Heterocyclen und Phenothiazinderivate
- O,P,N-haltige Heterocyclen (z.B. Cyclophosphamid)

[0050] Die folgenden Arzneistoffe (als Salz, Ester, Ether oder in freier Form) sind beispielsweise für eine Einarbeitung geeignet:

Analgetika/Antirheumatika
BTM Basen wie Morphin, Codein, Piritamid, Fentanyl und Fentanylderivate, Levomethadon, Tramadol, Diclofenac, Ibuprofen, Indometacin, Naproxen, Piroxicam, Penicillamin

Antiallergika
Pheniramin, Dimetinden, Terfenadin, Astemizol, Loratidin, Doxylamin, Meclozin, Bamipin, Clemastin

Antibiotika/Chemotherapeutika
hiervon: Polypeptidantibiotika wie Colistin, Polymyxin B, Teicplanin, Vancomycin; Malariamittel wie Chinin, Halofantrin, Mefloquin, Chloroquin, Virustatika wie Ganciclovir, Foscarnet, Zidovudin, Aciclovir und andere wie Dapson, Fosfomycin, Fusafungin, Trimetoprim

Antiepileptika
Phenytoin, Mesuximid, Ethosuximid, Primidon, Phenobarbital, Valproinsäure, Carbamazepin, Clonazepam

Antimykotika

a) intern:
Nystatin, Natamycin, Amphotericin B, Flucytosin, Miconazol, Fluconazol, Itraconazol
b) extern außerdem:
Clotrimazol, Econazol, Tioconazol, Fenticonazol, Bifonazol, Oxiconazol, Ketoconazol, Isoconazol, Tolnaftat

Corticoide (Interna)
Aldosteron, Fludrocortison, Betametason, Dexametason, Triamcinolon, Fluocortolon, Hydroxycortison, Prednisolon, Prednyliden, Cloprednol, Methylpredinsolon

Dermatika

a) Antibiotika:
Tetracyclin, Erythromycin, Neomycin, Gentamycin, Clindamycin, Framycetin, Tyrothricin, Chlortetracyclin, Mipirocin, Fusidinsäure
b) Virustatika wie oben, außerdem:

Podophyllotoxin, Vidarabin, Tromantadin
c) Corticoide wie oben, außerdem:
Amcinonid, Fluprednidin, Alclometason, Clobetasol, Diflorason, Halcinonid, Fluocinolon, Clocortolon, Flumetason, Diflucortolon, Fludroxycortid, Halometason, Desoximetason, Fluocinolid, Fluocortinbutyl, Fluprednidin, Prednicarbat, Desonid

Diagnostika

a) radioaktive Isotope wie Te99m, In111 oder I131, kovalent gebunden an Lipide oder Lipoide oder andere Moleküle oder in Komplexen
b) hochsubstituierte iodhaltige Verbindungen wie z.B. Lipide

Hämostyptika/Antihämorrhagika
Blutgerinnungsfaktoren VIII, IX

Hypnotika, Sedativa
Cyclobarbital, Pentobarbital, Phenobarbital, Methaqualon (BTM), Benzodiazepine (Flurazepam, Midazolam, Nitrazepam, Lormetazepam, Flunitrazepam, Triazolam, Brotizolam, Temazepam, Loprazolam)

Hypophysen-, Hypothalamushormone, regulatorische Peptide und ihre Hemmstoffe
Corticotrophin, Tetracosactid, Choriongonadotropin, Urofollitropin, Urogonadotropin, Somatropin, Metergolin, Bromocriptin, Terlipressin, Desmopressin, Oxytocin; Argipressin, Ornipressin, Leuprorelin, Triptorelin, Gonadorelin, Buserelin, Nafarelin, Goselerin, Somatostatin

Immuntherapeutika und Zytokine
Dimepranol-4-acetatamidobenzoat, Thymopentin, α-Interferon, β-Interferon, γ-Interferon, Filgrastim, Interleukine, Azathioprin, Ciclosporin

Lokalanaesthetika

intern:
Butanilicain, Mepivacain, Bupivacain, Etidocain, Lidocain, Articain, Prilocain,
extern außerdem:
Propipocain, Oxybuprocain, Tetracain, Benzocain

Migränemittel
Proxibarbal, Lisurid, Methysergid, Dihydroergotamin, Clonidin, Ergotamin, Pizotifen

Narkosemittel
Methohexital, Propofol, Etomidat, Ketamin, Alfentanil, Thiopental, Droperidol, Fentanyl

Nebenschilddrüsenhormone, Calciumstoffwechselregulatoren Dihydrotachysterol, Calcitonin, Clodronsäure, Etidronsäure

Opthalmika
Atropin, Cyclodrin, Cyclopentolat, Homatropin, Tropicamid, Scopolamin, Pholedrin, Edoxudin, Idouridin, Tromantadin, Aciclovir, Acetazolamid, Diclofenamid, Carteolol, Timolol, Metipranolol, Betaxolol, Pindolol, Befunolol, Bupranolol, Levobununol, Carbachol, Pilocarpin, Clonidin, Neostimgin

Psychopharmaka
Benzodiazepine (Lorazepam, Diazepam), Clomethiazol

Schilddrüsentherapeutika
1-Thyroxin, Carbimazol, Thiamazol, Propylthiouracil

Sera, Immunglobuline, Impfstoffe

a) Immunglobuline allgemein und spezifisch wie Hepatitis-Typen, Röteln, Cytomegalie, Tollwut, FSME, Varicella-Zoster, Tetanus, Rhesusfaktoren
b) Immunsera wie Botulismus-Antitoxin, Diphterie, Gasbrand, Schlangengift, Skorpiongift
c) Impfstoffe wie Influenza, Tuberkulose, Cholera, Diphterie, Hepatitis-Typen, FSME, Röteln, Hämophilus influenzae, Masern, Neisseria, Mumps, Poliomyelitis, Tetanus, Tollwut, Typhus

Sexualhormone und ihre Hemmstoffe
Anabolika, Androgene, Antiandrogene, Gestagene, Estrogene, Antiestrogene (Tamoxifen etc.)

Zystostatika und Metastasenhemmer

a) Alkylantien wie Nimustin, Melphalan, Carmustin, Lomustin, Cyclophosphamid, Ifosfamid, Trofosfamid, Chlorambucil, Busulfan, Treosulfan, Prednimustin, Thiotepa
b) Antimetabolite wie Cytarabin, Fluorouracil, Methotrexat, Mercaptopurin, Tioguanin
c) Alkaloide wie Vinblastin, Vincristin, Vindesin
d) Antibiotika wie Aclarubicin, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Plicamycin
e) Komplexe von Nebengruppenelementen (z. B. Ti, Zr, V, Nb, Ta, Mo, W, Ru, Pt) wie Carboplatin, Cisplatin und Metallocenverbindungen wie Titanocendichlorid
f) Amsacrin, Dacarbazin, Estramustin, Etoposid, Hydroxycarbamid, Mitoxanthron, Procarbazin, Temiposid
g) Alkylamidophospholipide (beschrieben in J. M. Zeidler, F. Emling, W. Zimmermann und H.

J. Roth, Archiv der Pharmazie, 324 (1991), 687)

h) Etherlipide wie Hexadecylphosphocholin, Ilmofosin und Analoga, beschrieben in R. Zeisig, D. Arndt und H. Brächwitz, Pharmazie 45 (1990), 809-818.

[0051] Insbesondere sind zu nennen: Cyclosporine, wie Cyclosporin A, und Cyclosporinderivate sowie Paclitaxel.

[0052] Als Polymer kann die erfindungsgemäße Zubereitung übliche Polymere aufweisen, wie beispielsweise Polyacrylate oder Polymethacrylate (Eudragit E, L, F), Cellulosen und Cellulosederivate (Methylhydroxypropylcellulose, Ethylcellulose, Hydroxypropylcellulose, acetatsuccinat (Aquoat®) oder natürliche Polymere (Schellack, Wachse, Bienenwachs, Glanz-Wachse). Durch die Wahl des Polymers kann die Freisetzungseigenschaft der Zubereitung oder der daraus hergestellten größeren Matrixeinheiten gesteuert werden. So kann durch Einsatz von Methylhydroxypropylcellulose eine im Vergleich zu nicht retardierten Tabletten nur gering verzögerte Freisetzung des Wirkstoffs erreicht werden. Die Verwendung von Eudragit E als Polymer führt zu einer verzögerten Freisetzung des Wirkstoffs bereits im Magen. Weist die Zubereitung Eudragit L bzw. F als Polymer auf, so ist eine kontrollierte Freisetzung des Wirkstoffs erst im Darmbereich möglich.

[0053] Als Lipid kann die erfindungsgemäße Zubereitung übliche Lipide aufweisen, wie beispielsweise natürliche, halbsynthetische und synthetische Triglyceride oder deren Mischungen, Mono- und Diglyceride allein oder in Mischung untereinander oder mit z.B. Triglyceriden, natürliche und synthetische Wachse, Fettalkohole einschließlich ihrer Ester und Ether sowie Lipidpeptide. Insbesondere sind synthetische Mono-, Di- und Triglyceride als Einzelsubstanzen oder in Mischung (z.B. Hartfett), Glycerintrifettsäureester (z.B. Glycerintrilaurat, -myristat, -palmitat, -stearat und -behenat) und Wachse wie z.B. Cetylpalmitat und Cera alba (gebleichtes Wachs, DAB9), Bienenwachs (z.B. Apifil; Apifac geeignet.

[0054] Weitere Lipide, zum Teil mit zusätzlich emulgierenden (SE = self emulsifying; selbstemulgierend) Eigenschaften sind Glycerinbehenat (z.B. Compritol 888 ATO), Glycerintribehenat (Compritol 888), Palmitostearate wie z.B. Glycerinpalmitostearat (z.B. Biogapress Vegetal ATO BM 297, Precirol Ato 5, Geleol), Diethylenglykol-, Propylenglykol-, Ethylenklykol-, Polyglykol- und Propylenglykolpalmitostearat, Stearate wie Glycerinstearat (z.B. Precirol WL 2155 Ato) und Polyglykolstearat, Isostearate, Polyalkohol-Fettsäureester (z.B. Compritol WL 3284), PEG-Behenat (z.B. Compritol HD5 ATO), Cetylpalmitat (z.B. Precifac Ato), Sacharoseester wie Saccharose-Monodistearat und -Monopalmitat (z.B. Sucro-Ester W.E. 15), Saccharose-Distearat (z.B. Sucro-Ester W.E. 7), Polyglycerinester wie Polyglycerinisostearostearat (Lafil WL 3254) und -palmitostearat, Polyglykolisierte Glyceride (z.B. Gelucire, Labrafil, Suppocire), selbstemulgierendes Polyglykolstearat (z.B. Superpolystate), selbstemulgierendes Polyglykolpalmitostearat (z.B. Tefose Serie), Glyceride C_{12}-C_{18} Fettsäuren (z.B. Lipocire) sowie deren Mischungen aus zwei oder mehr Lipiden.

[0055] Durch die Wahl des Lipids kann die Freisetzungseigenschaft der Zubereitung oder der daraus hergestellten größeren Matrixeinheiten gesteuert werden. So kann durch Einsatz von im Darm gut abbaubaren Lipiden die Freisetzung beschleunigt werden, da zusätzlich zur Freisetzung aufgrund von Diffusion aus der Matrix auch Freisetzung aufgrund vom Matrixerosion erfolgt. Mit langsamer abbaubaren Lipiden oder nicht im Magen-Darm-Trakt abbaubaren Lipiden erfolgt die Freisetzung verzögerter. Als relativ schnell durch Pankreas Lipase/Colipase abbaubares Lipid wird Dynasan 114 beschrieben, der Abbau Dynasan 118 erfolgt langsamer (C.Olbrich, R.H. Müller, Proceed. Int. Symp. Controlled Rel. Bioact. Mater., Stockholm, 921-922, 1997).

[0056] Als Hilfsstoffe können insbesondere die folgenden Stoffgruppen verwendet werden:

[0057] Füllstoffe aus dem Bereich der Zucker, wie beispielsweise Disaccharide (Laktose, Saccharose), Monosaccharide (Glukose, Fruktose) oder Polysaccharide (Stärken, Mais- oder Kartoffelstärke, Cellulose, natürliches Cellulosepulver, mikrokristalline Cellulose), Zukkeralkohole, wie beispielsweise Sorbit oder Mannit, oder Calciumphosphate.

[0058] Bindemittel, wie Polyvinylpyrrolidon (PVP, Kollidon CL), Gelatine, Stärkekleister, Cellulosen, Celluloseether oder Zucker.

[0059] Erfindungsgemäß ist festgestellt worden, daß eine Zubereitung in Form eines polymerhaltigen/lipidhaltigen Compounds, die eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine polymere phase/lipide Phase mit wenigstens einem Polymer/Lipid aufweist, wobei die Polymerphase/Lipidphase der Zubereitung inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist, erhalten wird, wenn die verschiedenen Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Polymerphase/Lipidphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend sprühgetrocknet wird.

[0060] Hierbei wird insbesondere eine Zubereitung erhalten, deren Polymerphase/Lipidphase frei von Hilfs- und/oder Wirkstoffphase ist.

[0061] Ebenso ist es möglich, die Suspension in einem Fließbett- oder Wirbelschichttrockner zu trocknen. Dabei werden die Phasen der Zubereitung wiederum zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst, wobei die Polymerphase/Lipidphase in der Flüssigkeit nicht löslich ist, und diese Suspension wird anschließend in einem Fließbett- oder Wirbelschichttrockner getrocknet.

[0062] Zur Durchführung des erfindungsgemäßen

Verfahrens werden die entsprechenden Mengen an Polymer/Lipid und Hilfsstoff und/oder Wirkstoff in einer Flüssigkeit mit Hilfe eines hochtourigen Rührers oder eines Dispergators suspendiert oder suspendiert und gelöst, wobei das Polymer/Lipid, im Gegensatz zu den bekannten Verfahren mit Polymerverarbeitung, in der Flüssigkeit nicht lösbar ist, sondern als Festoffpartikel vorliegt. In Abhängigkeit von dem zu suspendierenden Polymer/Lipid ist darauf zu achten, daß bei der Dispergierung keine zu hohen Scherkräfte und Temperaturen auftreten, die zu einer Aggregation bzw. einem Zusammenfließen von Polymerpartikeln/Lipidpartikeln führen.

[0063] Die verwendete Flüssigkeit ist insbesondere demineralisiertes Wasser oder ein wäßriges oder organisches Dispersions- bzw. Suspensionsmittel.

[0064] Die jeweils gewünschte Viskosität der im Sprühtrockner, Fließbett- oder Wirbelschichttrockner zu versprühenden Suspension wird über den prozentualen Feststoff-Anteil gesteuert. Zusätzliche Regulationsmöglichkeiten bestehen bei wasserlöslichen Hilfsstoffen über deren Konzentration und chemische Natur (z. B. Lactose, Hilfsstoffe mit ausgeprägtem viskositätserhöhenden Effekt).

[0065] Eine weitere vorteilhafte Ausgestaltung ist der Zusatz von Netzmittel und/oder Bindemittel und/oder Weichmacher (z.B. Triethylcitrat, Propylenglycol, u.a) zur Suspension. Als Bindemittel sind insbesondere Polyvinylpyrrolidon, Gelatine, Stärkekleister, Cellulose, Celluloseether oder Zucker geeignet. Sie erhöhen die mechanische Festigkeit der Zubereitung. Der Weichmacher erlaubt einen validierungsfähigen Einfluß auf die Plastizität, Verformbarkeit und Verfilmbarkeit des Polymers/Lipids und ermöglicht damit die Steuerbarkeit der Freigabe des Wirkstoffs neben dem Retard-Effekt des Polymers/Lipids an sich. Als Weichmacher können vor allem Triethylcitrat und Propylenglycol eingesetzt werden. Aber auch andere innere und äußere Weichmacher, die als übliche Zusätze zu Polymeren/Lipiden bekannt sind, sind zur Steuerung der Wirkstofffreisetzung geeignet.

[0066] Die Suspension wird anschließend bei Sprühdrücken üblicherweise über 20 bar mit Hilfe geeigneter Ein- und Mehrstoff-Düsen im Sprühturm bei geeigneten Abluft-Temperaturen, in Abhängigkeit von der Sensibilität der Wirk- und Hilfsstoffe sowie von den apparativen Gegebenheiten des Sprühturmes und dessen Peripherie, sprühgetrocknet oder im Fließbett- oder Wirbelschichttrockner getrocknet.

[0067] Die erhaltene Zubereitung kann anschließend, soweit es erforderlich ist, noch nachgetrocknet werden. Hierbei ist eine Nachtrocknung und/oder eine zusätzliche Agglomeration der Zubereitung auf Fließbett- oder Wirbelschichttrocknern möglich.

[0068] Aufgrund des Trocknungsvorgangs im Sprühtrockner, Fließbettoder Wirbelschichttrockner weist die erhaltene Zubereitung eine angenähert sphärische Form auf.

[0069] Es ist erfindungsgemäß erkannt worden, daß die beschriebene Zubereitung, die eine inkohärente Polymerphase/Lipidphase und eine kohärente Hilfsstoff- und/oder Wirkstoffphase aufweist, sich zur Verwendung bei der Herstellung von größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften eignet. Hierbei können sämtliche bekannte Verfahren angewendet werden, so daß größere Matrixeinheiten jeder beliebigen Form erhalten werden, wie beispielsweise Tabletten, Pellets oder zylinderförmige Stäbchen. Ebenso können mit der erfindungsgemäßen Zubereitung die bekannten Verfahren zur Herstellung von Extrusionsoder Sphäronisationspellets oder zur Abfüllung der Zubereitung in Kapseln durchgeführt werden.

[0070] Ferner ist erkannt worden, daß sich die erfindungsgemäße Zubereitung insbesondere zur Herstellung von größeren Matrixeinheiten und/oder Tabletten mit kontrollierten Freisetzungseigenschaften mittels Direkttablettierung eignet. Dies ist trotz des hohen Polymeranteils/Lipidanteils der Zubereitung möglich, da durch das erfindungsgmäße Verfahren unter anderem eine sehr gute Fließeigenschaft und ein verbessertes Komprimierverhalten der Zubereitung erreicht wird.

[0071] Vorteilhaft ist insbesondere die Herstellung von Tabletten mit-. tels Direkttablettierung aus einer wirkstofffreien Zubereitung, die mit wenigstens einem Wirkstoff und bei Bedarf mit weiteren Hilfsstoffen gemischt wird, sowie aus einer wirkstoffhaltigen Zubereitung, die unter Umständen zusätzlich noch mit wenigstens einem Wirkstoff und soweit erforderlich mit weiteren Hilfsstoffen gemischt werden kann.

[0072] Neben den üblichen Tabletten sind insbesondere auch Drageekerne, Film- oder Manteltablettenkerne oder zylinderförmige Stäbchen durch Direkttablettierung bzw. direkte Komprimierung erhältlich.

[0073] Ferner kann die erfindungsgemäße Zubereitung zur Herstellung größerer Matrixeinheiten verwendet werden, die verschiedene Wirkstoffe oder den gleichen Wirkstoff in unterschiedlichen Dosen aufweisen (z. B. Schichttabletten), wobei jeder Wirkstoff oder jede Dosis einen eigenen, von den anderen Wirkstoffen oder Dosen unabhängigen Freisetzungszeitpunkt aufweist. Hierzu wird eine wirkstoffhaltige erfindungsgemäße Zubereitung, die auch zusätzlich noch wenigstens einen Hilfsstoff aufweisen kann, mit wenigstens einem weiteren oder demselben Wirkstoff, falls erforderlich unter Zusatz von Hilfsstoffen, wie beispielsweise Füll-, Formtrenn- oder Bindemitteln, gemischt. Die Mischung wird dann mittels Direkttablettierung oder nach anderen bekannten Verfahren zu größeren Matrixeinheiten verarbeitet. Dies ist besonders bei inkompatiblen Wirkstoffen vorteilhaft, da diese Vorgehensweise zu einer räumlichen Trennung der Wirkstoffe in der Arzneiform führt.

[0074] Durch die Verwendung der erfindungsgemäßen Zubereitung in einem Verfahren zur Herstellung von größeren Matrixeinheiten werden Modifikationen des Freisetzungsprofils ermöglicht, da der oder die Wirkstoffe in der größeren Matrixeinheit unterschiedlich stark als Funktion der Polymermenge/Lipidmenge eingeschlos-

sen sind und somit unterschiedlich schnell freigesetzt werden.

[0075] Die erfindungsgemäße Verwendung der Zubereitung zur Direkttablettierung weist insbesondere den Vorteil auf, daß die Wirkstoffe und/oder Hilfsstoffe durch den angewandten Trocknungsvorgang gegenüber der herkömmlichen Feuchtgranulierung, die bisher als Vorstufe zur Komprimierung von polymerhaltigen Zubereitungen erforderlich gewesen ist, nur sehr kurze Zeit der Feuchtigkeit ausgesetzt werden. Die Temperaturbelastung ist bei den genannten Trockungsverfahren steuerbar und sogar auszuschalten, wenn im Luftstrom bei Raumtemperatur getrocknet wird.

[0076] Zur Herstellung größerer Matrixeinheiten nach bekannten Verfahren sei beispielsweise die Herstellung von Pellets angeführt. Dazu wird die erfindungsgemäße Zubereitung unter Zusatz adäquater Hilfsstoffe mit einem für die Pelletherstellung üblichen Extruder extrudiert und über eine anschließende Sphäronisation in Kügelchen von Pelletgröße überführt. Alternativ kann die Herstellung über einen Lochwalzenkompaktor mit angeschlossenem Pelltierbehälter erfolgen. Mögliche Geräte sind Spheronizer® und Marumizer®. Ebenso können diese Pellets durch Einsatz eines Pelletiertellers aus der beschriebenen Zubereitung hergestellt werden.

[0077] Diese Pellets können ebenso wie die Zubereitung selbst beispielsweise in Kapseln abgefüllt oder zu größeren Einheiten verpreßt werden.

[0078] Die Erfindung wird im folgenden anhand von Ausführungsbeispielen und Figuren näher erläutert. Alle Prozentangaben beziehen sich auf das Gewicht.

Beispiele

1. Herstellung einer Lactose-Ethylcellulose-Zubereitung (50:50):

[0079] Beide Komponenten werden mit Hilfe eines Rührers in demineralisiertem Wasser dispergiert. Die Dispersion wird bei einem Feststoffgehalt von bis zu 40 Prozent und einem Sprühpumpen-Druck von 30-50 bar in einem Labor-Sprühturm bei Abluft-Temperaturen zwischen 70 und 100 Grad Celsius versprüht.

[0080] Das Ergebnis ist ein gut fließfähiges Sprüh-Agglomerat bestehend aus Lactose und Ethylcellulose in einer Korngrößenverteilung zwischen 1 und 630 µm, wobei der Hauptanteil von 50-80% zwischen 63 und 400 µm liegt.

[0081] Die so hergestellte Zubereitung zeichnet sich insbesondere aufgrund ihres Merkmals, daß die polymere Phase inkohärent und die Hilfsstoff- und/oder Wirkstoffphase kohärent ist, sowie ihrer angenähert sphärischen Form und ihrer Oberflächenbeschaffenheit (Kavitäten, Lakose) als sehr gut mit Wirkstoff misch- und beladbar aus.

[0082] Bei lipophilen Wirkstoffen kann die Freisetzungsdauer der Wirkstoffe bei direkter Mischung mit der Zubereitung bis zum Faktor drei gegenüber nicht retardierten Tabletten verlängert werden. Die Freisetzungsdauer kann wiederum durch Veränderung des Polymer-Anteiles in der Tablettiermasse, z.B. durch.Zumischen eines Füllstoffes der Typen Stärke und Laktose variiert werden.

2. Herstellung einer Acetylsalicylsäure (ASS) aufweisenden Lactose-Ethylcellulose-Zubereitung:

[0083] Die Herstellung erfolgt wie in 1. beschrieben, die Mischung der Komponenten Lactose:Ethylcellulose: ASS erfolgt im Gewichtsverhältnis 45:45:10.

3. Herstellung einer Tablette aus einer Acetylsalicylsäure (ASS) aufweisenden Zubereitung:

[0084] Die unter 1. hergestellte wirkstofffreie Lactose-Ethylcellulose-Zubereitung wird mit ASS im Verhältnis 90:10 gemischt, der Mischung wird 0,5% Aerosil und 1% Magnesiumstearat zugesetzt und direkttablettiert.

4. Herstellung einer Tablette aus eine Acetylsalicylsäure (ASS) aufweisenden Zubereitung:

[0085] Der unter 2. hergestellten ASS-beladenen Lactose-Ethylcellulose-Zubereitung werden 0,5% Aerosil und 1% Magnesiumstearat zugesetzt und direkttablettiert.

5. Herstellung einer Paracetamol-Lactose-Ethylcellulose-Zubereitung (20:40:40):

[0086] Alle Komponenten werden in demineralisiertem Wasser dispergiert und auf eine gewünschte pumpen- und druckabhängige Vikosität eingestellt. Es erfolgt die Versprühung nach den oben beschriebenen Verfahren. Die so hergestellte Zubereitung ist aufgrund ihrer Pulvereigenschaften unmittelbar für die Direkttablettierung geeignet, wobei durch den variabel einstellbaren Prozentanteil an Polymer - durch Zumischung von weiteren Hilfsstoffen, variable Tablettenhärte - die Freigabe des Wirkstoffes im gewünschten Umfang verzögert werden kann.

6. Herstellung eines Compritol-Trehalose-Compounds:

[0087] Compritol 888 ATO (Glyceroltribehenat) wurde geschmolzen, in heißes Wasser nach Zusatz von 1,2% Poloxamer 188 eingegossen und darin mittels eines hochtourigen Ultra-Turrax dispergiert. Nach Erkalten wurde in der wäßrigen Lipidpartikeldispersion Trehalose gelöst, so daß sich als Endkonzentration 10% Lipid und 3 % Trehalose ergab. Diese Mischung wurde in einem Mini-Büchi sprühgetrocknet (Inlet-Temperatur: 110 °C, Outlet-Temperatur: 50°C; Sprüh-Flow: 600 Normliter). Es wurde ein rieselfähiges Lipid-Hilfsstoff-Compound erhalten.

7. Herstellung einer Tablette aus Compound mit 1% Paracetamol:

[0088] 9 Teile des in Beispiel 1 beschriebenen Lipid-Trehalose-Compounds wurde unter Zusatz von 0,1 Teil Paracetamol und unter Zumischung von 0,5% Aerosil 200 und 0,5% Magnesiumstearat auf einer Korsch-Excenterpresse direkt komprimiert. Tablettensollgewicht 505 mg.

8. Herstellung einer Tablette aus Compound mit 10% Paracetamol:

[0089] 13 Teile des in Beispiel 6 beschriebenen Lipid-Trehalose-Compounds wurden mit 3 Teilen Trehalose gemischt, dieser Mischung 10% Paracetamol zugesetzt und unter Zumischung von 0,5% Aerosil 200 und 0,5% Magnesiumstearat auf einer Korsch-Excenterpresse direkt komprimiert. Tablettensollgewicht 505 mg.

9. Freisetzung aus einer Tablette aus Compound mit 10% Paracetamol:

[0090] Die Freisetzung von Paracetamol aus der in Beispiel 8 hergestellten Tablette wurde mit der Paddle-Methode nach der United States Pharmacopeia bestimmt, Freisetzungsmedium: Wasser, Temperatur 37 °C. Die erhaltenen Freisetzungskurven zeigen Figur 5 und 6.

Kurze Erläuterung der Figuren:

Figur 1:

[0091] In Figur 1 ist die Herstellung einer erfindungsgemäßen Zubereitung über ein Compound nach dem erfindungsgemäßen Verfahren dargestellt: Der Matrixbildner (z.B. Polymerpartikel/Lipidpartikel) wird in Wasser dispergiert, der Hilfsstoff und/oder Wirkstoff wird ebenfalls in der Wasserphase gelöst bzw. dispergiert und die Suspension wird versprüht, wobei das Wasser durch Trocknen entfernt wird. Es entsteht eine Zubereitung, die selbst aus kleinen Polymerpartikeln/Lipidpartikeln zusammengesetzt ist, wobei die Zwischenräume mit dem Hilfsstoff (links oder mit Hilfsstoff- und Wirkstoff gefüllt sind (rechts). Die Zubereitung weist eine inkohärente polymere/lipide Phase und eine kohärente Hilfs- und/oder Wirkstoffphase auf.

Figur 2:

[0092] Figur 2 zeigt ein Beispiel für die Verwendung der erfindungsgemäßen Zubereitung zur Herstellung größerer Matrixeinheiten. Die wirkstofffreie Zubereitung (z.B. aus Polymer und Lactose bzw. aus Lipid und Flowlac 100- sprühgetrocknete Lactose, Fa. Meggle, Deutschland) wird mit dem Wirkstoff (in Pulverform) gemischt, gegebenenfalls Tablettierhilfsstoffe soweit erforderlich zugesetzt und die Mischung direkttablettiert.

Figur 3a:

[0093] Aus dem Stand der Technik bekanntes O/W-Emulsionsverfahren: Hier ist ein Tropfen eines organischen Lösungsmittels mit darin gelöstem Matrixbildner (z.B. Polymer) in einer Wasserphase dispergiert (O/W-Emulsion), wobei der Wirkstoff in der organischen Phase gelöst (links) oder bei unlöslichem Wirkstoff dispergiert ist (rechts). Weitere Erklärung siehe Text.

Figur 3b:

[0094] Aus dem Stand der Technik bekanntes W/O-Emulsionsverfahren: Hier ist ein Tropfen Wasser mit darin gelöstem Matrixbildner (z.B. wasserlösliches Polymer) in einer organischen Phase dispergiert (O/W-Emulsion), wobei der Wirkstoff in der wäßrigen Phase gelöst (links) oder bei unlöslichem Wirkstoff dispergiert ist (rechts). Weitere Erklärung siehe Text.

Figur 4:

[0095] Figur 4 zeigt das erfindungsgemäße Verfahren zur Herstellung der erfindungsgemäßen Zubereitung. Die polymere Phase/Lipidphase ist nicht gelöst, sondern in Wassertropfen dispergiert bzw. suspendiert, die durch Sprühen in einer Gasphase verteilt werden. Ein Hilfsstoff (z.B. Lactose, links) oder ein Hilfsstoff und ein Wirkstoff (rechts) sind ebenfalls im Wassertropfen gelöst oder dispergiert bzw. suspendiert. Nach Entfernen des Wassers entsteht eine wirkstofffreie Hilfsstoff-Polymer/Lipid-Zubereitung (links) oder eine Wirkstoff-Hilfsstoff-polymer/Lipid-zubereitung (rechts), wobei die polymere Phase/Lipidphase in beiden Fällen inkohärent ist.

Figuren 5 und 6:

[0096] Freisetzung von Paracetamol aus einer Tablette bei Verwendung der erfindungsgemäßen Zubereitung (Beispiel 4). Darstellung der freigesetzten Menge als Funktion der Zeit (Figur 5) und als Funktion der Wurzel aus der Zeit (Figur 6).

Patentansprüche

1. Zubereitung in Form eines matrixmaterialhaltigen Compounds mit einer Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder einer Wirkstoffphase mit wenigstens einem Wirkstoff, **dadurch gekennzeichnet, daß** das Matrixmaterial ausgewählt ist aus Polymeren, wobei im Fall von Cellulosematerialien diese Cellulosematerialien Cellulosederivate sind, und Lipiden, die Polymerphase und/oder die Lipidphase der Zubereitung inkohärent und die

Hilfs- und/oder Wirkstoffphase der Zubereitung kohärent ist.

2. Zubereitung in Form eines matrixmaterialhaltigen Compounds mit einer Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder einer Wirkstoffphase mit wenigstens einem Wirkstoff, **dadurch gekennzeichnet, daß** das Matrixmaterial ausgewählt ist aus Polymeren, wobei im Fall von Cellulose der Anteil der Matrixmaterialphase der Zubereitung 70 bis 98% beträgt, und Lipiden, die Polymerphase und/oder die Lipidphase der Zubereitung inkohärent und die Hilfs- und/oder Wirkstoffphase der Zubereitung kohärent ist.

3. Zubereitung nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Matrixmaterialphase der Zubereitung Hilfs- und/oder Wirkstoff enthält oder frei davon ist.

4. Zubereitung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 1 bis 98% beträgt.

5. Zubereitung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 10 bis 95% beträgt.

6. Zubereitung nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung mehr als 15% und höchstens 90% beträgt.

7. Zubereitung nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 40 bis 70% beträgt.

8. Zubereitung nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, daß** die polymere Phase ein Polyacrylat und/oder ein Polymethacrylat und/oder die Lipidphase natürliche, halbsynthetische und synthetische Triglyceride oder deren Mischungen, Mono- und Diglyceride allein oder in Mischung untereinander oder mit Triglyceriden, natürliche und synthetische Wachse, Fettalkohole einschließlich ihrer Ester und Ether sowie Lipidpeptide, insbesondere synthetische Mono-, Di- und Triglyceride als Einzelsubstanzen oder in Mischung, speziell Hartfett, Glycerintrifettsäureester, speziell Glycerintrilaurat, -myristat, -palmitat, -stearat und -behenat, und Wachse, speziell Cetylpalmitat und Cera alba (gebleichtes Wachs, DAB9), Bienenwachs enthält.

9. Zubereitung nach einem der Ansprüche 1 bis 8, **dadurch gekennzeichnet, daß** die Polymerphase ein Polyacrylat und/oder ein Polymethacrylat, ein Cellulosederivat oder natürliches Polymer und/oder die Lipidphase natürliches Lipid enthält.

10. Zubereitung nach einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, daß** sie mindestens einen Wirkstoff enthält.

11. Zubereitung nach einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet, daß** die Hilfsstoffphase wenigstens einen Füllstoff, insbesondere ausgewählt aus Monosacchariden, Disacchariden, Polysacchariden, Zuckeralkoholen und Calciumphosphat, und/oder wenigstens ein Bindemittel, insbesondere ausgewählt aus Polyvinylprrolidon, Gelatine, Stärkekleister, Cellulosen, Celluloseethern und Zuckern aufweist.

12. Zusammensetzung nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** sie in Form eines durch Direktkomprimierung herstellbaren Preßlings vorliegt.

13. Verfahren zur Herstellung einer Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, daß** die Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Matrixmaterialphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend sprühgetrocknet wird.

14. Verfahren zur Herstellung einer Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, daß** die Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Matrixmaterialphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend in einem Fließbett- oder Wirbelschichttrockner getrocknet wird.

15. Verfahren nach Anspruch 13 oder 14, **dadurch gekennzeichnet, daß** die Flüssigkeit ein wäßriges oder organisches Suspensionsmittel ist.

16. Verfahren nach einem der Ansprüche 13 bis 15, **dadurch gekennzeichnet, daß** der Suspension wenigstens ein Bindemittel und/oder wenigstens ein Netzmittel und/oder wenigstens ein Weichmacher zugesetzt wird.

17. Verwendung der Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12 zur Herstellung von größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften nach bekannten Verfahren.

18. Verwendung der Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der An-

sprüche 1 bis 12 zur Herstellung von Tabletten und/ oder größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften mittels Direkttablettierung.

Claims

1. Preparation in the form of a compound containing a matrix material with an auxiliary-substance phase comprising at least one auxiliary substance and/or an active-substance phase comprising at least one active substance, **characterized in that** the matrix material is selected from polymers, where, in the case of cellulose materials, these cellulose materials are cellulose derivatives, and lipids, where the polymer phase and/or the lipid phase of the preparation is incoherent and the auxiliary-substance phase and/or active-substance phase of the preparation is coherent.

2. Preparation in the form of a compound containing a matrix material with an auxiliary-substance phase comprising at least one auxiliary substance and/or an active-substance phase comprising at least one active substance, **characterized in that** the matrix material is selected from polymers, where, in the case of cellulose, the proportion of the matrix-material phase of the preparation is from 70 to 98%, and lipids, where the polymer phase and/or the lipid phase of the preparation is incoherent and the auxiliary-substance phase and/or active-substance phase of the preparation is coherent.

3. Preparation according to Claim 1 or 2, **characterized in that** the matrix-material phase of the preparation comprises an auxiliary substance and/or active substance or is free therefrom.

4. Preparation according to one of Claims 1 to 3, **characterized in that** the proportion of the matrix-material phase in the preparation is from 1 to 98%.

5. Preparation according to one of Claims 1 to 4, **characterized in that** the proportion of the matrix-material phase in the preparation is from 10 to 95%.

6. Preparation according to one of Claims 1 to 5, **characterized in that** the proportion of the matrix-material phase in the preparation is greater than 15% and at most 90%.

7. Preparation according to one of Claims 1 to 6, **characterized in that** the proportion of the matrix-material phase in the preparation is from 40 to 70%.

8. Preparation according to one of Claims 1 to 7, **characterized in that** the polymeric phase comprises a polyacrylate and/or a polymethacrylate, and/or the lipid phase comprises natural, semisynthetic and synthetic triglycerides or mixtures thereof, mono- and diglycerides, alone or in a mixture with one another or with triglycerides, natural and synthetic waxes, fatty alcohols, including esters thereof, and ethers, as well as lipid peptides, in particular synthetic mono-, di- and triglycerides as individual substances or in the form of a mixture, especially hydrogenated fat, glycerol trifatty acid esters, especially glycerol trilaurate, trimyristate, tripalmitate, tristearate and tribehenate, and waxes, especially cetyl palmitate and cera alba (bleached wax, DAB9), or beeswax.

9. Preparation according to one of Claims 1 to 8, **characterized in that** the polymer phase comprises a polyacrylate and/or a polymethacrylate, a cellulose derivative or natural polymer, and/or the lipid phase comprises natural lipid.

10. Preparation according to one of Claims 1 to 9, **characterized in that** it comprises at least one active substance.

11. Preparation according to one of Claims 1 to 10, **characterized in that** the auxiliary-substance phase comprises at least one filler, in particular selected from monosaccharides, disaccharides, polysaccharides, sugar alcohols and calcium phosphate, and/or at least one binder, in particular selected from polyvinylpyrrolidone, gelatine, starch glue, celluloses, cellulose ethers and sugars.

12. Composition according to one of the preceding claims, **characterized in that** it is in the form of a pressing which can be produced by direct compression.

13. Process for the production of a preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12, **characterized in that** the phases of the preparation are suspended or suspended and dissolved together in a liquid, where the matrix-material phase is insoluble in the liquid, and this suspension is subsequently spray-dried.

14. Process for the production of a preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12, **characterized in that** the phases of the preparation are suspended or suspended and dissolved together in a liquid, where the matrix-material phase is insoluble in the liquid, and this suspension is subsequently dried in a fluidized-bed drier.

15. Process according to Claim 13 or 14, **character-**

ized in that the liquid is an aqueous or organic suspension medium.

16. Process according to one of Claims 13 to 15, **characterized in that** at least one binder and/or at least one wetting agent and/or at least one plasticizer is added to the suspension.

17. Use of the preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12 for the production of larger matrix units having controlled release properties by known processes.

18. Use of the preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12 for the production of tablets and/or larger matrix units having controlled release properties by means of direct tabletting.

Revendications

1. Composition sous la forme d'un composite contenant un matériau de matrice avec une phase agent auxiliaire contenant au moins un agent auxiliaire et/ou une phase principe actif contenant au moins un principe actif, **caractérisée en ce que** le matériau de matrice est choisi parmi les polymères, dans lesquels, lorsqu'il s'agit de matériaux cellulosiques, ces matériaux cellulosiques sont des dérivés de la cellulose, et parmi les lipides, et **en ce que** la phase polymère et/ou la phase lipidique de la préparation est incohérente et la phase agent auxiliaire et/ou la phase principe actif de la préparation est cohérente.

2. Composition sous la forme d'un composite contenant un matériau de matrice avec une phase agent auxiliaire contenant au moins un agent auxiliaire et/ou une phase principe actif contenant au moins un principe actif, **caractérisée en ce que** le matériau de matrice est choisi parmi les polymères, dans lesquels, dans le cas de la cellulose, la proportion de la phase matériau de matrice de la préparation est de 70 à 98%, et parmi les lipides, et **en ce que** la phase polymère et/ou la phase lipidique de la préparation est incohérente et la phase agent auxiliaire et/ou la phase principe actif de la préparation est cohérente.

3. Composition selon la revendication 1 ou 2, **caractérisée en ce que** la phase matériau de matrice de la préparation contient un agent auxiliaire et/ou un principe actif ou bien en est dépourvue.

4. Composition selon l'une des revendications 1 à 3, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 1 à 98%.

5. Composition selon l'une des revendications 1 à 4, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 10 à 95%.

6. Composition selon l'une des revendications 1 à 5, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est supérieure à 15% et au maximum égale à 90%.

7. Composition selon l'une des revendications 1 à 6, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 40 à 70%.

8. Composition selon l'une des revendications 1 à 7, **caractérisée en ce que** la phase polymère contient un polyacrylate et/ou un polyméthacrylate et/ou **en ce que** la phase lipidique contient des triglycérides naturels, semi-synthétiques et synthétiques ou des mélanges de ceux-ci, des mono- et diglycérides seuls ou mélangés entre eux ou avec des triglycérides, des cires naturelles et synthétiques, des alcools gras, y compris leurs esters et leurs éthers, ainsi que des peptides lipidiques, en particulier des mono-, di- et triglycérides synthétiques seuls ou en mélange, notamment des graisses durcies, des triesters d'acides gras avec le glycérol, en particulier les trilaurate, trimyristate, tripalmitate, tristéarate et tribéhénate de glycérol, et des cires, notamment le palmitate de cétyle et la cire blanche (Cera alba, DAB9), la cire d'abeilles.

9. Composition selon l'une des revendications 1 à 8, **caractérisée en ce que** la phase polymère contient un polyacrylate et/ou un polyméthacrylate, un dérivé de la cellulose ou un polymère naturel et/ou **en ce que** la phase lipidique contient un lipide naturel.

10. Composition selon l'une des revendications 1 à 9, **caractérisée en ce qu'**elle contient au moins un principe actif.

11. Composition selon l'une des revendications 1 à 10, **caractérisée en ce que** la phase agent auxiliaire contient au moins une matière de charge, en particulier choisie parmi les monosaccharides, les disaccharides, les polysaccharides, les alcools de sucres et le phosphate de calcium, et/ou au moins un liant, en particulier choisi parmi la polyvinylpyrrolidone, la gélatine, la colle d'amidon, les celluloses, les éthers de cellulose et les sucres.

12. Composition selon l'une au moins des revendications précédentes, **caractérisée en ce qu'**elle se présente sous la forme d'une pièce moulée suscep-

tible d'être obtenue par compression directe.

13. Procédé de fabrication d'une composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12, **caractérisé en ce que** les phases de la composition sont mises en suspension ensemble dans un liquide ou bien mises en suspension et dissoutes, la phase matériau de matrice n'étant pas soluble dans le liquide, et cette suspension est ensuite séchée par pulvérisation.

14. Procédé de fabrication d'une préparation sous la forme d'un compound contenant un matériau de matrice selon l'une des revendications 1 à 12, **caractérisé en ce que** les phases de la préparation sont mises en suspension ensemble dans un liquide ou bien mises en suspension et dissoutes, la phase matériau de matrice n'étant pas soluble dans le liquide, et cette suspension est ensuite séchée dans un sécheur à lit fluidisé.

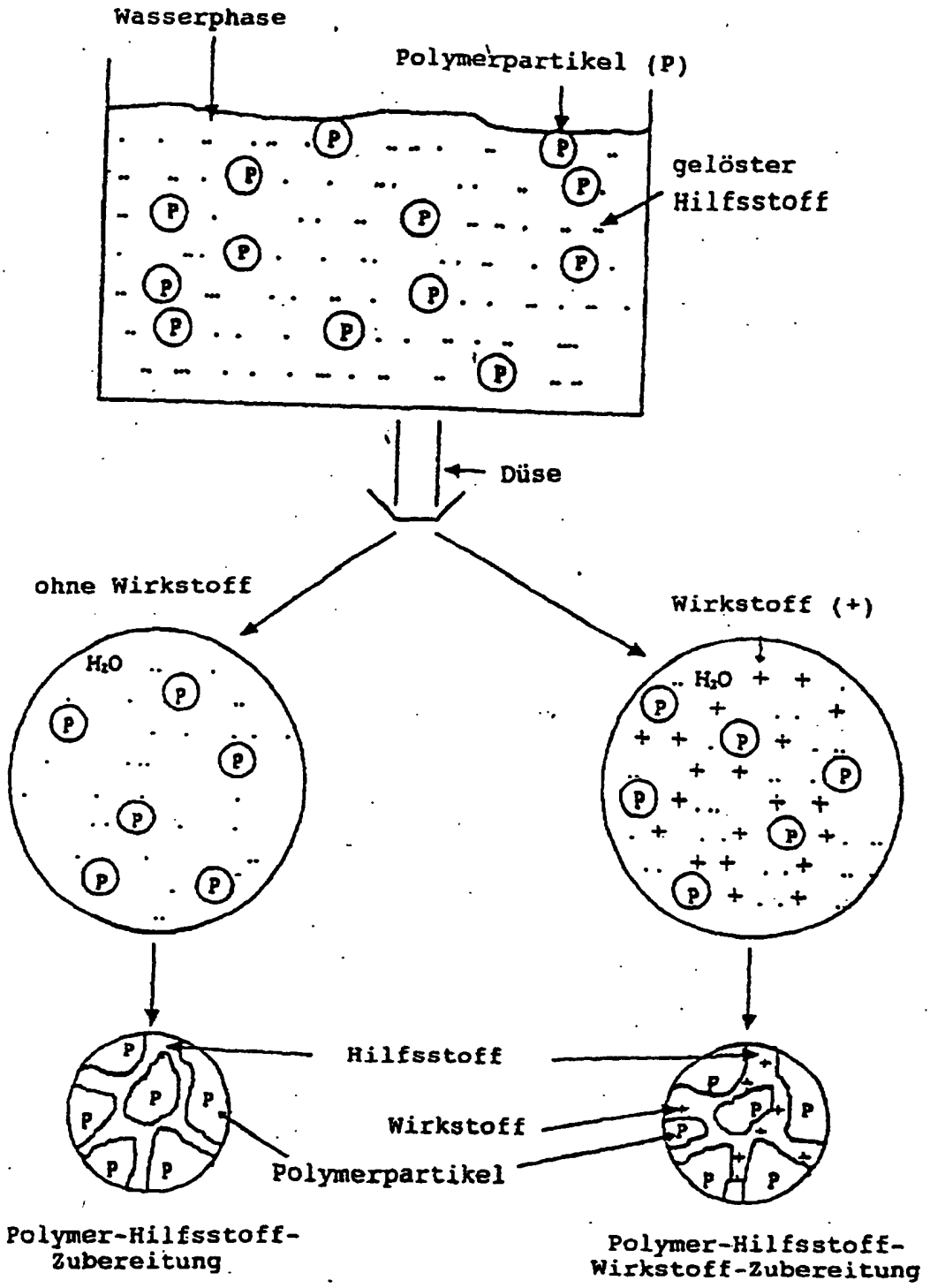
15. Procédé selon la revendication 13 ou la revendication 14, **caractérisé en ce que** le liquide est un agent de suspension aqueux ou organique.

16. Procédé selon l'une des revendications 13 à 15, **caractérisé en ce que** l'on ajoute à la suspension au moins un liant et/ou au moins un agent mouillant et/ou au moins un plastifiant.

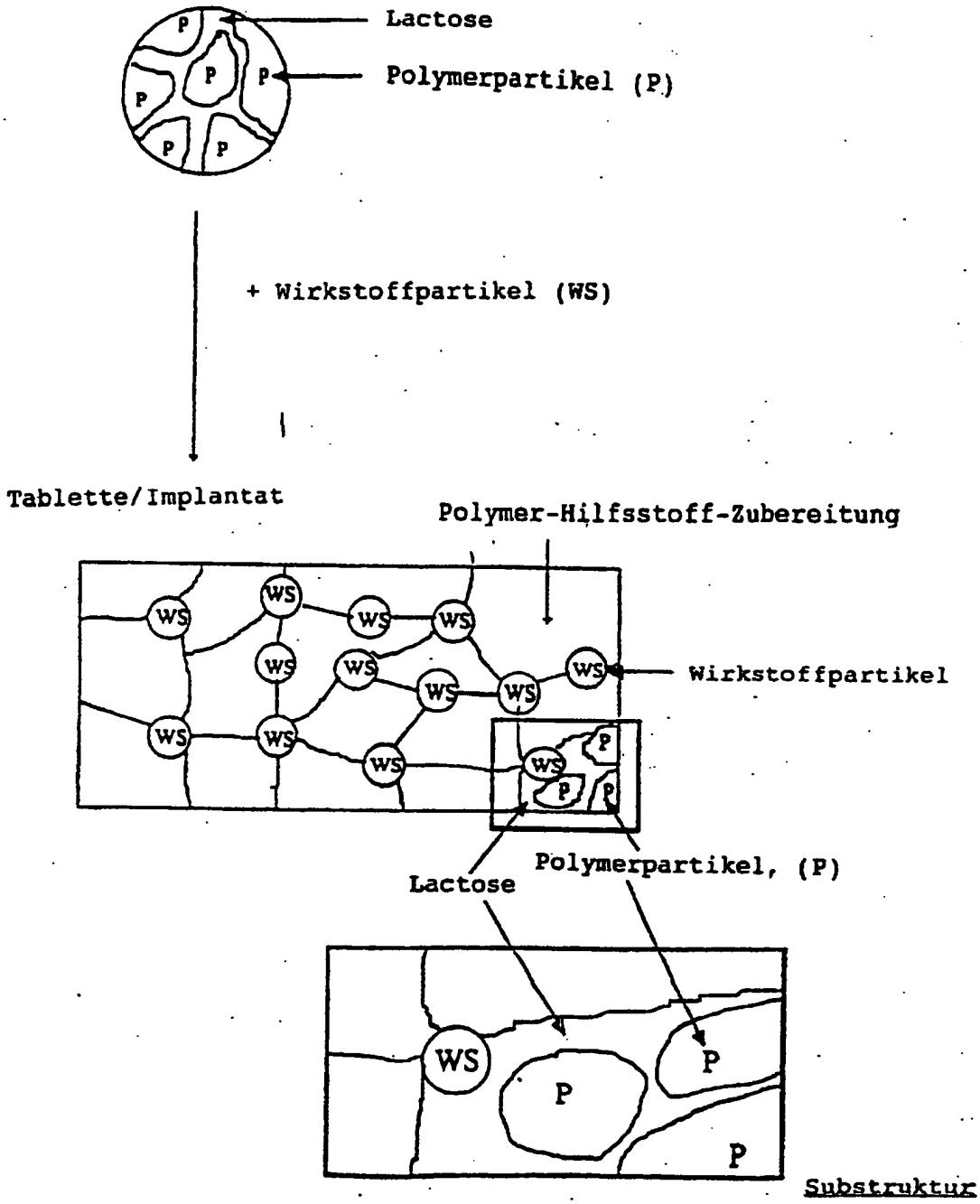
17. Utilisation de la composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12 pour la fabrication d'unités de matrice de plus grande taille ayant des propriétés de libération contrôlée selon des procédés connus.

18. Utilisation de la composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12 pour la fabrication de comprimés et/ou d' unités de matrice de plus grande taille ayant des propriétés de libération contrôlée par pastillage direct.

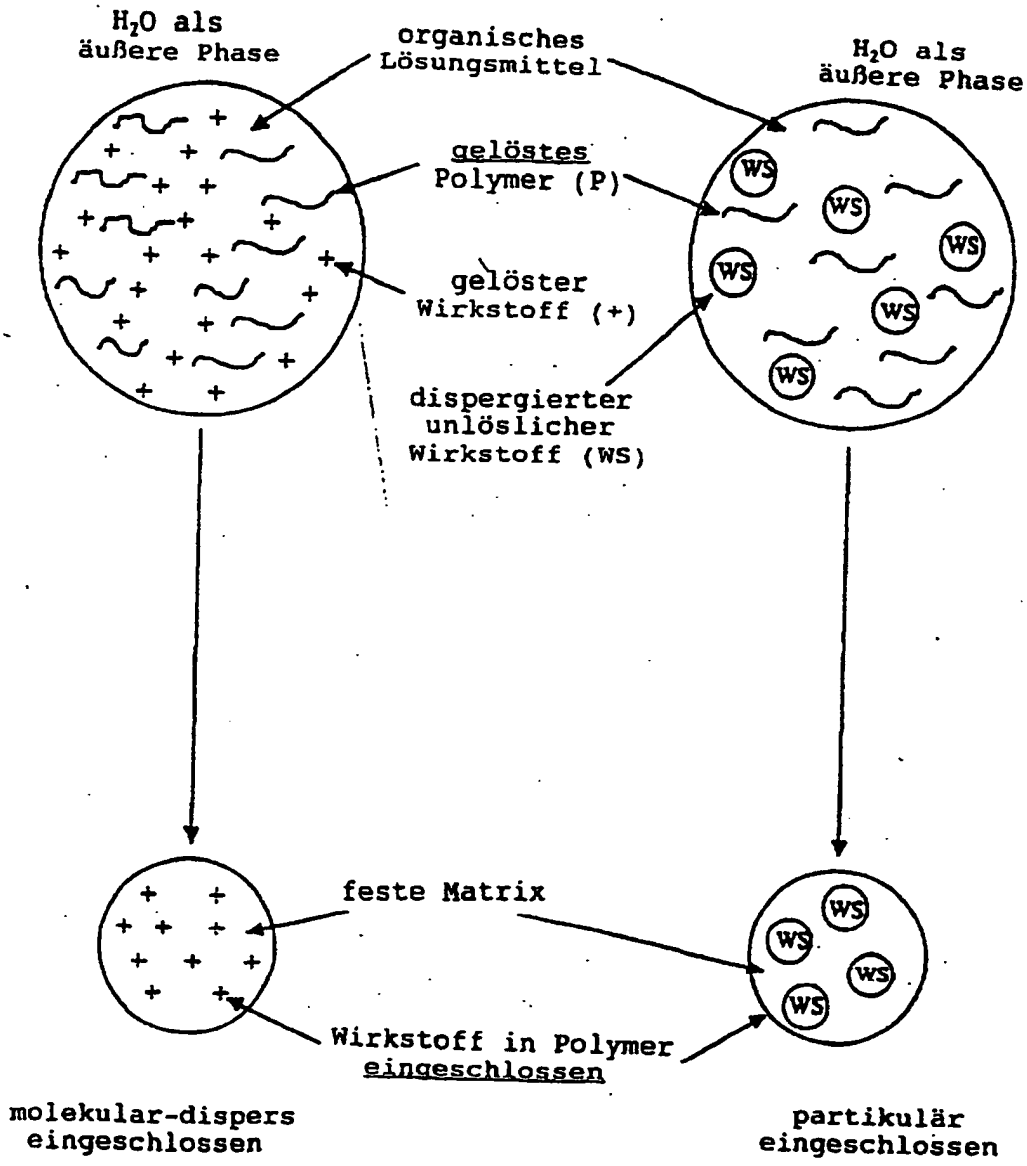
FIGUR 1: Herstellung der Zubereitung in Form eines Pellets



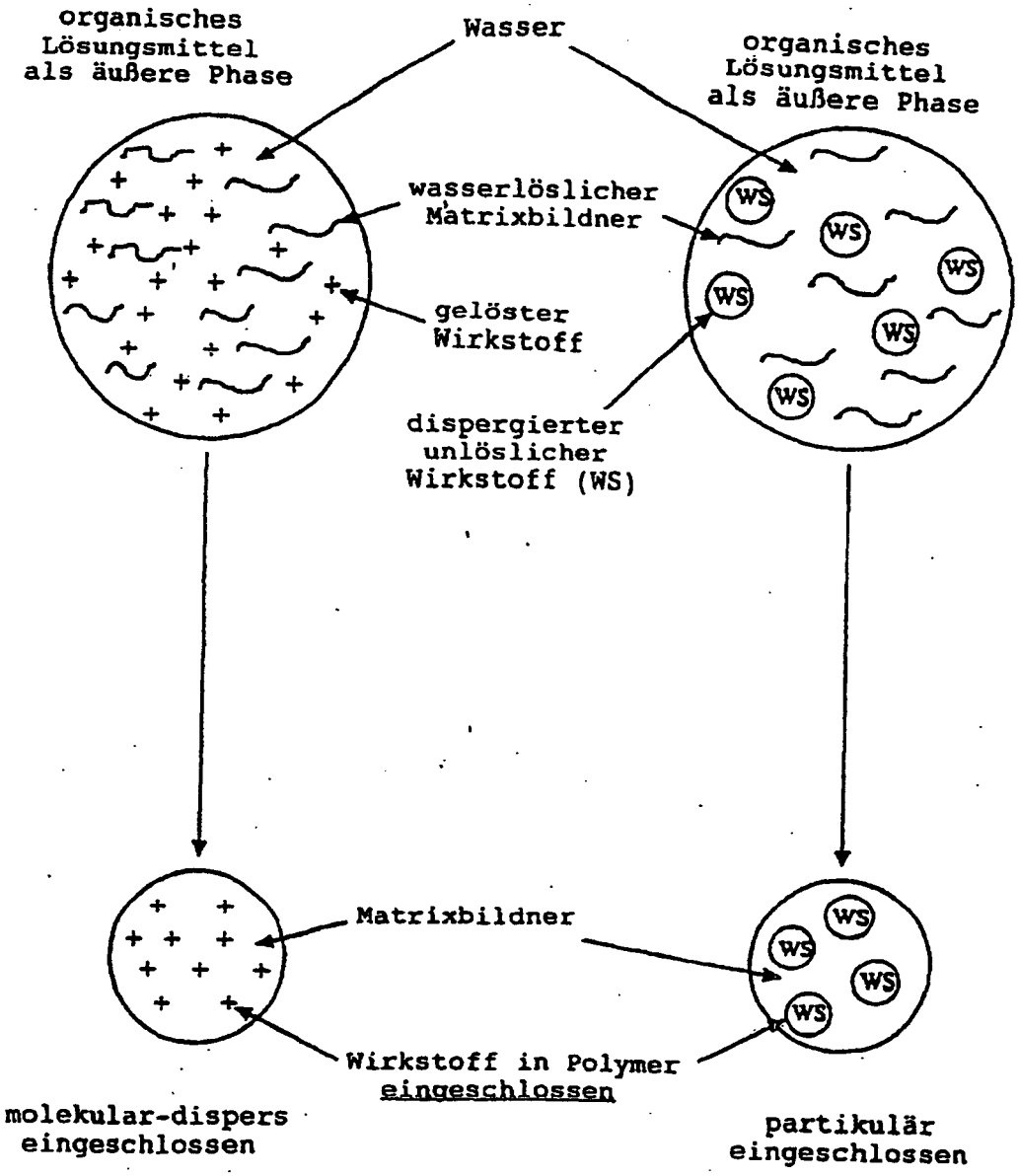
FIGUR 2: Herstellung größerer Matrixeinheiten



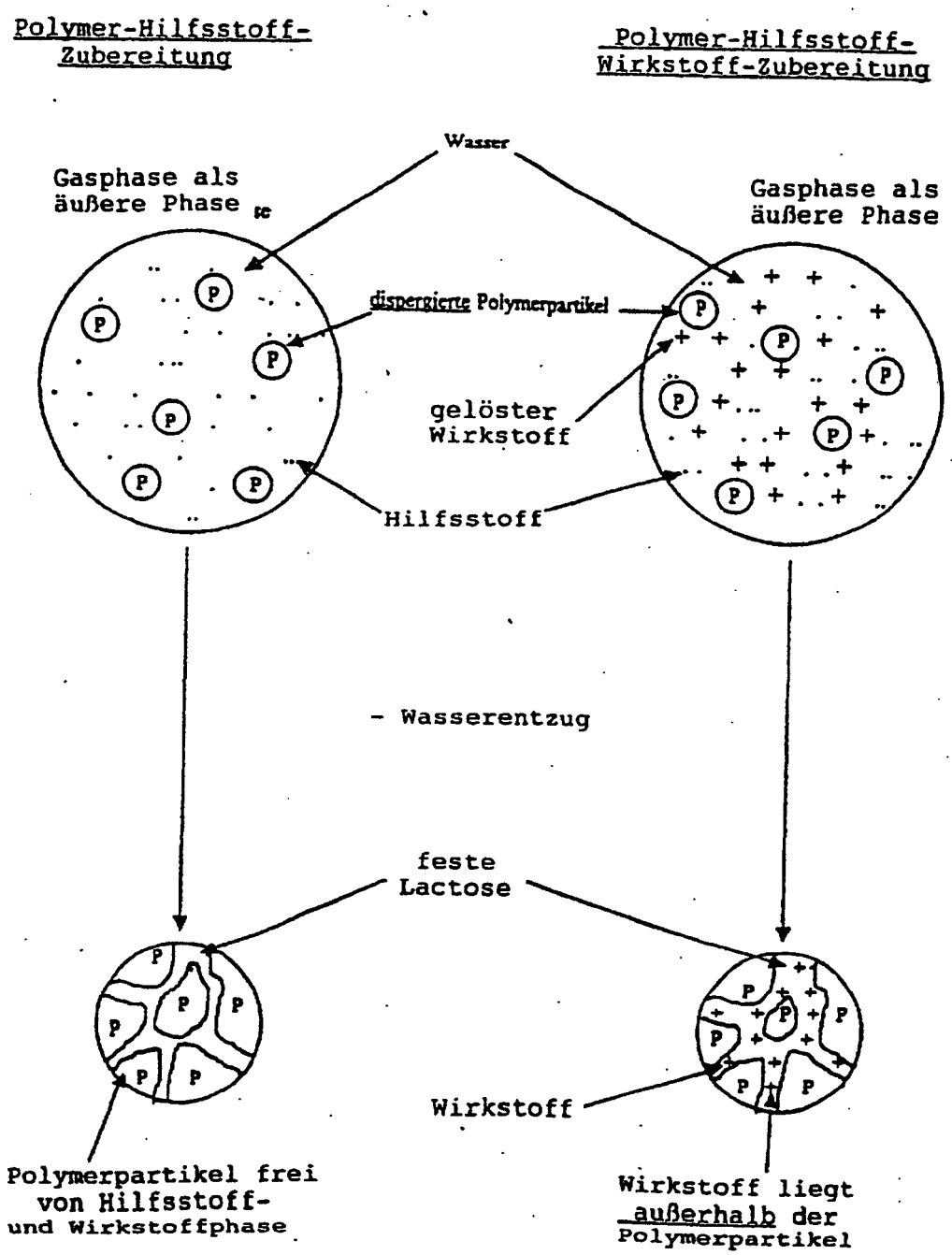
FIGUR 3a: O/W-Emulsionsverfahren (Stand der Technik)



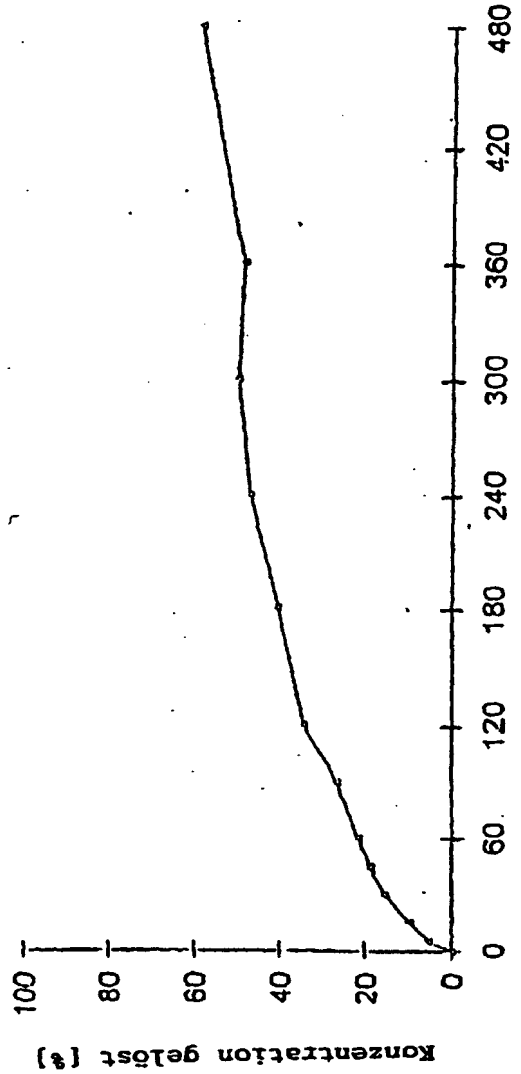
FIGUR 3b: W/O-Emulsionsverfahren (Stand der Technik)



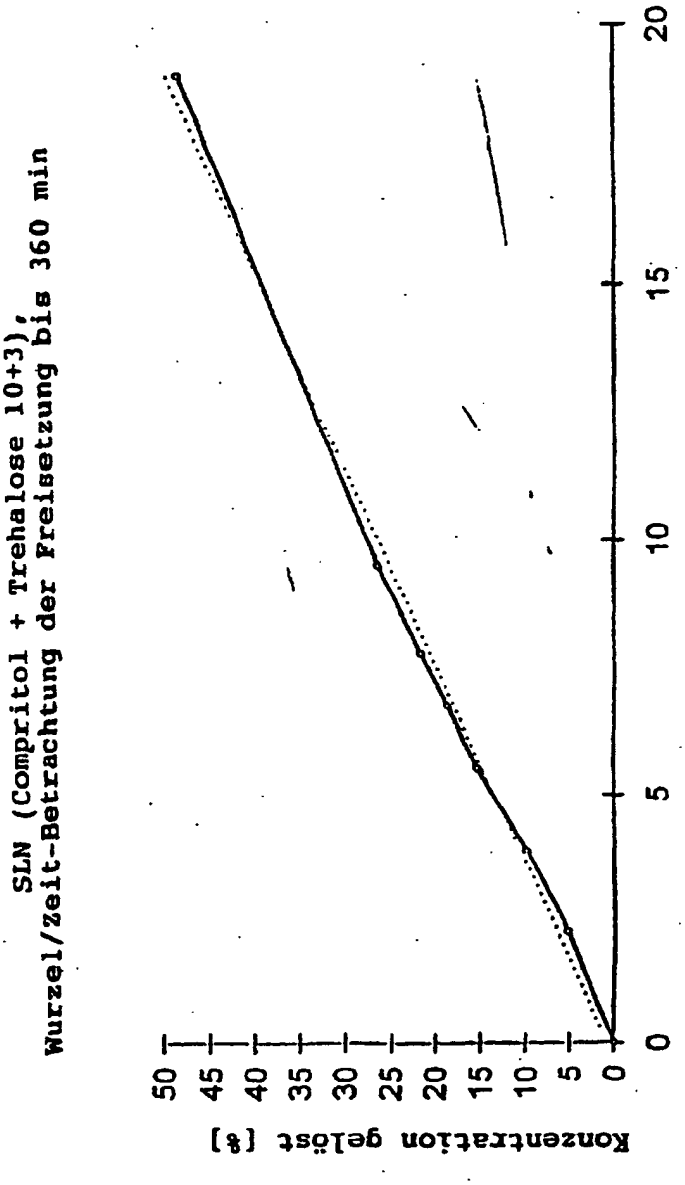
FIGUR 4: Erfindungsgemäßes Verfahren



Abbildungen zu Lipid-Compounds /1



Figur 5: Freisetzung von Paracetamol aus tablettierter Mischung aus sprühgetrocknetem Lipid-Trehalose-Compound (9 Teile) plus Paracetamol (1 Teil) unter Zumischung von 0,5 % Aerosil 200 und 0,5 % Magnesiumstearat. (Tablettengewicht: 500 mg, Zusammensetzung Lipid-Trehalose-Compound Compritol 888 ATO 10 Teile plus 3 Teile Trehalose).



Figur 6: Wurzel-Zeit Diagramm der Freisetzungskurve aus Figur 5 zur Belegung der Matrixfreisetzung (gestrichelte Linie = Trendlinie)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 957 073 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
17.11.1999 Bulletin 1999/46

(21) Application number: **98108608.5**

(22) Date of filing: **12.05.1998**

(51) Int. Cl.[6]: **C07C 1/00**, C07C 217/62, C07C 217/48, C07C 219/28, C07C 219/22, C07D 207/06, C07D 295/06, C07C 271/08, C07F 7/18, C07C 307/02, A61K 31/135, A61K 31/325, A61K 31/40, A61K 31/435

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

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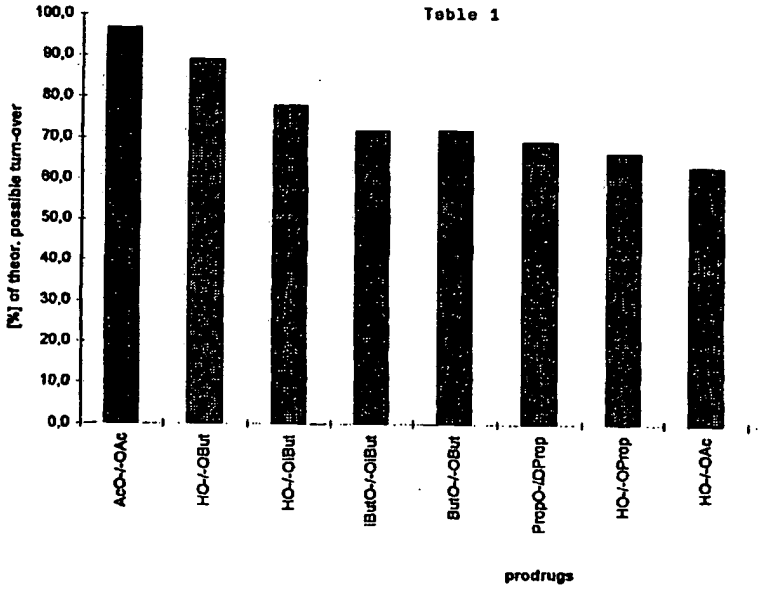
(54) Novel derivatives of 3,3-diphenylpropylamines

(57) The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



EP 0 957 073 A1

Printed by Xerox (UK) Business Services
2.16.7/3.6

Description

[0001] The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

[0002] More particularly, the present invention relates to certain prodrugs of 3,3-diphenylpropylamines while avoiding on administration to a mammal a high variation in bioavailability and formation of active metabolites which can result in a substantial variation in response - too low efficacy or too much side effects - for the subjects on the suggested therapy.

[0003] In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions but also the main part of the contractions in the overactive bladder resulting in symptoms as urinary frequency, urgency and urge incontinence. For this reason antimuscarinic drugs have been instituted as a treatment of bladder over activity.

[0004] Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder over activity. The effectiveness of oxybutynin has been demonstrated in several clinical studies but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the must common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

[0005] Tolterodine is a new, potent and competetive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al, 1997, Tolderodine - a new bladderselective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

[0006] A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite is almost identical to those of tolterodine (Nilvebrant et al, 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite give a major contribution to the clinical effect in most patients.

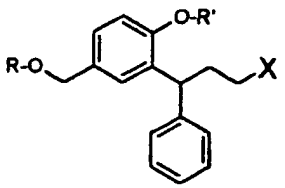
[0007] The document WO 94/11337 discloses that the active metabolite of tolterodine is suggested as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0008] However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability. In a method to circumvent this disadvantage different prodrugs of the metabolite have been synthetized and tested for their absorption/bioavailability data.

[0009] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is an further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption/bioavailability after oral administration of the drugs or an unfavourable metabolism.

[0010] The novel compounds of the present invention are represented by the general Formula (I)

(I)



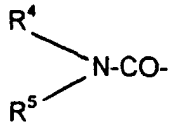
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

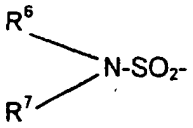
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting



of wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

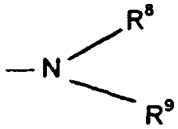
e) a group consisting



of wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

[0011] The compounds of Formula (I) can form salts with physiologically acceptable acids, organic and inorganic. Furthermore the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid

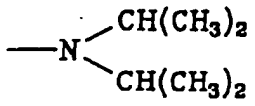
addition salts include the hydrochloride, hydrobromide and the like.

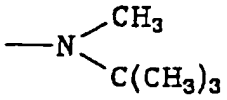
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

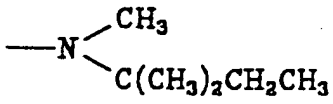
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

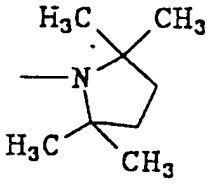
[0014] According to an other embodiment of the invention at least one of R^8 and R^9 comprises a branched carbon chain.

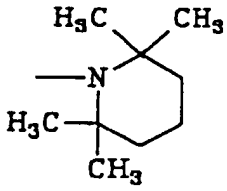
[0015] Presently preferred tertiary amino groups X in Formula I include the following groups a) to h):

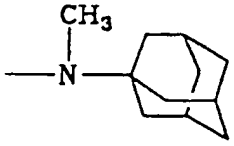
a) 

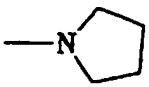
b) 

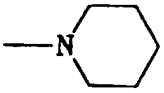
c) 

d) 

e) 

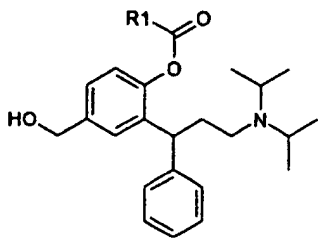
f) 

g) 

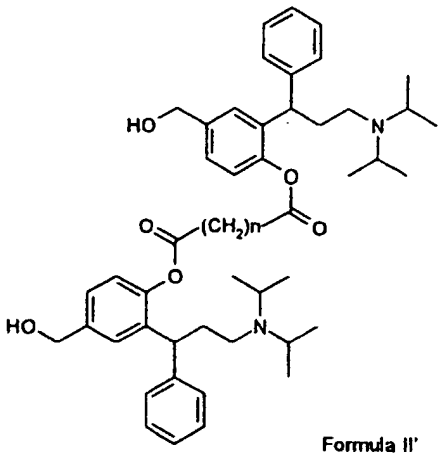
h) 

[0016] Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general Formulae II and II'



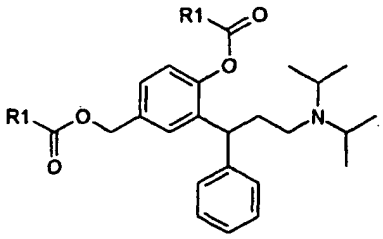
Formula II



Formula II'

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester

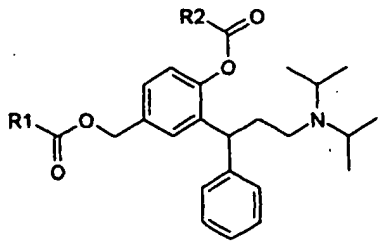
B) Identical diesters represented by the general Formula III



Formula III

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

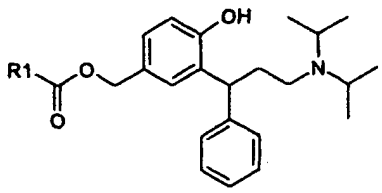
C) Mixed diesters represented by the general Formula IV



Formula IV

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

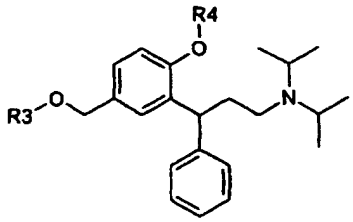
D) Benzylic monoesters represented by the general Formula V



Formula V

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester

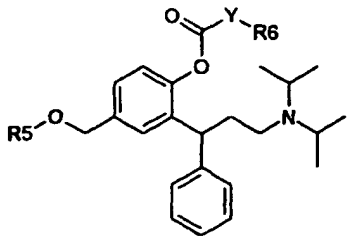
E) Ethers and silyl ethers represented by the general Formula VI



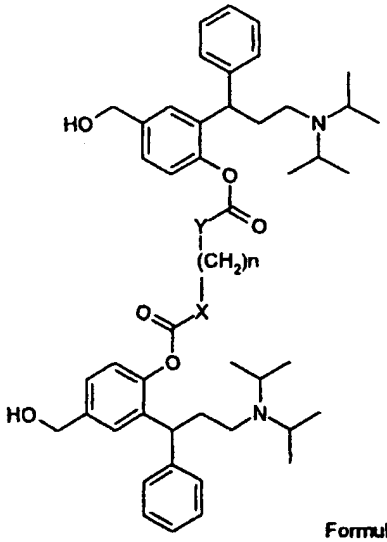
Formula VI

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
(4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester

F) Carbonates and carbamates represented by the general Formulae VII and VII'



Formula VII



Formula VII'

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester

N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

[0017] The compounds of formula (I) may, in accordance with the present invention be prepared by per se conventional methods. Methods for preparing substituted 3,3-diphenylpropylamines as disclosed by this invention may be synthesized according to methods as described in the document PCT/SE93/00927.

[0018] The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

[0019] The following starting materials and preffered Examples illustrate the invention:

I. Experimental

1. General

[0020] All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts reported (^{13}C NMR, ppm) refer to the solvents $CDCl_3$ (77.10 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm) respectively. Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution. Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%). Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.

2. Synthesis of Intermediates A and B

[0021] An icecooled solution of 4-bromophenol (69.2g) and cinnamoyl chloride (66.8g) in dichloromethane (150ml) was treated with triethylamine (40.6g). After stirring for 18h at room temperature the mixture was washed with water (250ml), 1M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0g, 99.8% yield), m.p. 113.3 °C, tlc (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

[0022] A portion of the ester (60.0g) was dissolved in a mixture of acetic acid (60ml) und concentrated sulphuric acid (18ml) and refluxed for 2h. After cooling, the reaction mixture was poured into ice water and the product was was isolated by extraction with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from boiling I ethanol (150ml) yielded 26.3g (43.8% yield) of pure, crystalline *6-bromo-4-phenylchroman-2-one,* m.p. 117.8 °C, tlc (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89. 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

[0023] A suspension consisting of 6-bromo-4-phenylchroman-2-one (85.0g), anhydrous potassium carbonate (46.7g), sodium iodide (20.5g) and benzyl chloride (40.6g) in methanol (350ml) and acetone (350ml) was refluxed for 3h. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300ml) and the extract was washed with water (2 x 200ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8g (102.1 % crude yield) of *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc (1) 0.77. NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77,126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

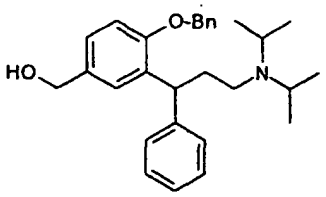
[0024] A solution of the propionate (121.0g) in 350ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9g) in tetrahydrofuran (350ml). After stirring at room temperature for 18h, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8 °C, tlc (1) 0.47, *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol.* NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

[0025] A cooled (5 °C) solution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0g) in dichloromethane (300ml) war treated with pyridine (79.4ml) and than p-toluenesulphonyl chloride (60.6g) in dichloromethane (200ml). After 18h at room temperature the solvent was removed in vacuum and the residue extracted diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3g, 93.6% yield), tlc (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

[0026] A solution of the toluenesulphonate (139.3g) in acetonitrile (230ml) and N,N-diisopropylamine (256g) was refluxed for 97h. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500ml) and aqueous sodium hydroxide (2M, 240ml). The organic phase was washed twice with water (250ml) and then extracted with 1M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5g, 77.9% yield), tlc (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70. 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

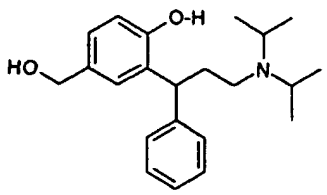
[0027] An ethereal Grignard solution, prepared from the above amine (22.8g), ethyl bromide (17.4g) and magnesium (6.1g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200ml) and then cooled to -60 °C. Powdered solid carbon dioxide (ca. 50g) was the added in small portions and the green reaction mixture was warmed at room temperature. After the addition of an aqueous solution of ammonium chloride (200ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide *4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzoic acid hydrochloride* (14.7g, 64.3% yield), m.p. 140 °C (dec.), tlc (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

[0028] The hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free base thus obtained (28g) was dissolved in dry diethyl ether (230ml). This solution was slowly (2h) dropped under an nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8g) in ether (140ml). After stirring for 18h, the reaction was quenched by the addition of water (4.7ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4 °C, tlc (2) 0.32, **Intermediate A**. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



(Intermediate A)

[0029] A solution of Intermediate A (9.1g) in methanol (100ml) was hydrogenated over Raney-nickel (4.5g) under ambient conditions. After 5h thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95g, 96.5% yield) which gradually solidified, *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50 °C, tlc (2) 0.15, **Intermediate B**. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38. Hydrochloride: colourless crystalls, m.p. 187-190 °C (with decomposition)



(Intermediate B)

3. Examples

a) Phenolic monoesters

aa) General Procedure

[0030] A stirred solution of *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (Intermediate B, 1.71g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of Formila II, 2.50 mmol for compounds of Formula II') in 60 ml of dichloromethane was cooled to 0 °C and then triethylamine (0.502g,4.96 mmol for compounds of Formula II, 1.05g, 9.92 mmol for compounds of Formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 mm. Stirring was continued for 18h at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and a low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents. The esters of Formula II or II' were obtained as viscous colourless to light yellow syrups in purities between 90% and 99% (tlc, HPLC, NMR).

bb) Salt formation (Example hydrochloride)

[0031] A cooled (0 °C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of Formula II) or 9.4 mmol (diamines of Formula II') ethereal (1M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100 °C (with decomposition).

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43(4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36;

2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92,

128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.42, 20.62, 36.95, 41.72, 42.27, 48.23, 64.83, 122.74, 125.33, 127.36, 127.89, 127.97, 128.38, 129.34, 130.64, 131.15, 131.83, 136.87, 138.90, 143.82, 147.74, 164.77

Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.38 (4); NMR (CDCl3): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.40 (4)
NMR (CDCl3): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 122.85, 127.39, 127.99, 128.35, 129.31, 131 .84, 136.98, 138.94, 143.80, 147.40, 147.40, 169.05

Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

[0032] Identical diesters (Formula III) were prepared and worked-up as described above with the exeption that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.65 (4) This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F: Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45 - 58 [1954])

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.76 (4);; GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GO-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$): 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80,65.21,123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; ; GO-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; ; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, R_f 0.83 (4); NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane,): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.69 (4); NMR (CDCl3): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

c) Mixed diesters

[0033] Mixed diesters (Formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Workup and physical properties corresponded to the bases and salts described above.

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.71, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18;

2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-*phenylpropyl)-benzyl ester*, R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

[0034] A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 h complete disappearence of the starting material (R_f = 0.45 (3). The mixture was filtered and then evaporated under high vacuum (< 40 °C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.26 (2); NMR ($CDCl_3$): 19.45,20.96, 33.26, 39.63, 42.27, 48.23, 48.23, 63.59, 118.00, 127.36, 128.33, 128.33, 128.48, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.77 (4); NMR ($CDCl_3$):18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

[0035] A mixture of Intermediate B (3.4g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^3-OH, (50 - 150 ml) was stirred at room temperature until no starting material was detectable (2 - 24 h). After evaporation to dryness (< 35 °C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100 - 200 ml, 5 %, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of Formula VI (R^4 = H) as colourless to light yellow oils.

[0036] Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for Examples of the structure of Formula IV.

Hydrochlorides:

[0037] Molar equivalents of bases of Formula VI (R^4 = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile to give colourless crystalline material.

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m. p. 161 °C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%); hydrochloride: m. p 158 - 161 °C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80. 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65

2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128.35, 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.10, 0.29, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14 155.06

Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134:00, 136.47, 144.16, 155.09

Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.48, 128.44, 133.37, 135.74, 144.11, 155.20

4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85), 470.43 (10%), 396.3 (31%)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

[3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl]-diisopropylamine, R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.87 (4); NMR ($CDCl_3$):20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05,137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01); GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and Carbonates

[0038] A solution of 4.0 mmol of Intermediate B or benzylic ether (Formula VI, R^4 = H) in dichloromethane (20 ml) was treated at room temperature for 16 h with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation the oily residue was redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides. Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65 °C over 18 h.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of Formula II to IV. Alkyl chloroformates were used as acylation reagents.

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m. p. 64 °C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester, R_f 0.36 (3), NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

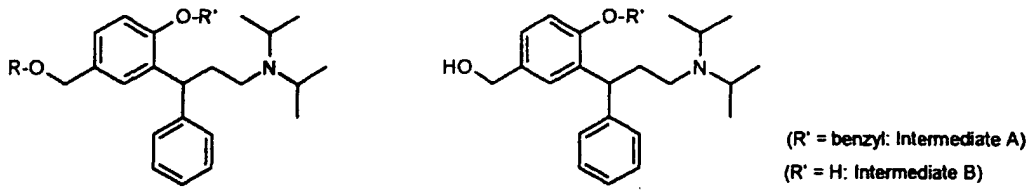
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, (Formula VII', X = Y = NH, n = 4) R_f 0.60 (6); dihydrochloride: m. p. 142.5 - 145.6 °C

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

4. The respective prodrugs (Formula I) or pharmaceutically acceptable salts thereof were prepared also from Intermediate A or Intermediate B by the following methods:

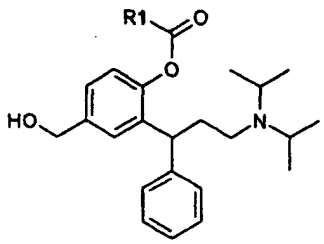
[0039]



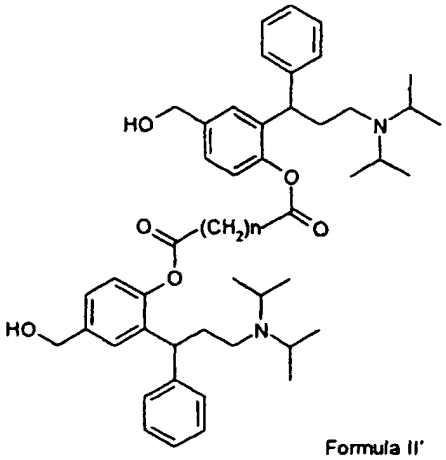
Formula I

a) Phenolic monoesters

[0040] Treatment of Intermediate B with an equivalent of an acylating agent (e.g. acyl halogenide or acyl anhydride) in an inert solvent and in the presence of an condensating agent (e.g. amine) provides phenolic monoesters of Formula II or Formula II' (n = 0-12), respectively, if polyfunctional acylating agents (e.g. acid chlorides of dicarboxylic acids) are used.



Formula II

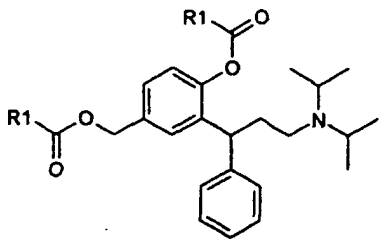


Formula II'

[0041] Alternatively, structures of Formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *„Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

b) Identical diesters

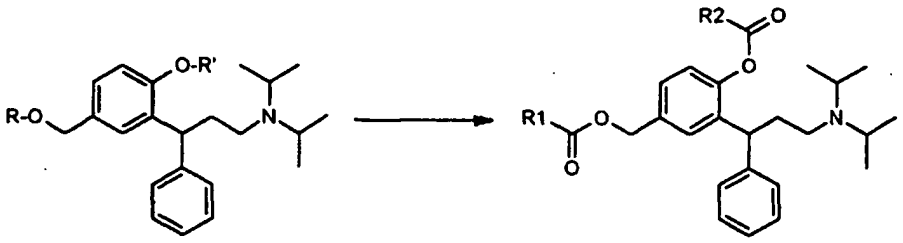
[0042] Di-acyl compounds are readily accessible if an at least two molar excess of acylation agent is used in the above-mentioned conversions of Intermediates A or B or, more general, on treatment of compounds of Formula I with acylating agents in the presence of suitable catalysts.



Formula III

c) Mixed diesters

[0043] Acylation of compounds of the general Formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions yields mixed diesters of Formula IV, where R^1 and R^2 are different.

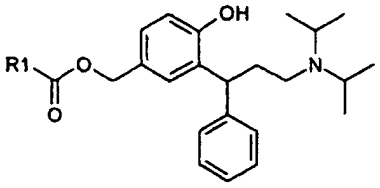


Formula I

Formula IV

d) Benzylic monoesters

[0044] Moreover, the invention refers to the preparation of phenols with *para* acyloxymethyl substituents (Formula V). These compounds can be prepared in several chemical steps from intermediates such as Formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P. G. M. Wuts, „*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, in the present invention that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

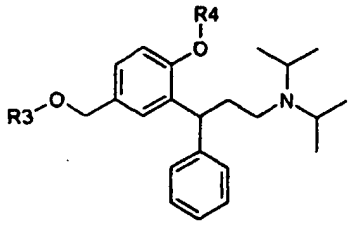


Formula V

e) Ethers and silanyl esters

[0045] Regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J. M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P. M. Deya; J. Org. Chem. 53: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or Formulas II or VI (in which R^3 hydrogen) or Formula VII (in which R^5 is hydrogen) as well as benzylic acylates such as Formula III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. 30: 1939-1942 [1989]).

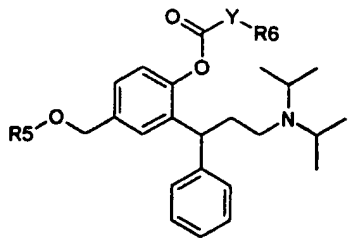
Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^4 = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis 1981, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta 76: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. 26: 4307-4310 [1987]).



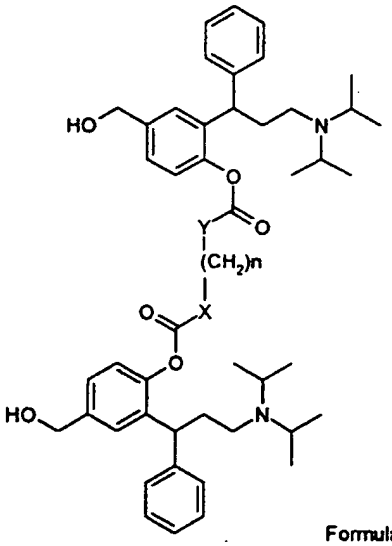
Formula VI

f) Carbamates and Carbonates

[0046] Other reactive reagents which can be used in the reaction of the hydroxy groups of Intermediates A or B, Formulas II, II', V, or VI (R^3 or R^4 = hydrogen) shown above are, for example, other activated carbonyl compounds or carbonyl precursor reagents. Preferably, haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates, isothiocyanates can be used. The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10 °C to the refluxing temperature of the solvent or reagent used to provide compounds of the general Formula VII where R^5 represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and Y and R^6 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of Formula VII' where X, Y have the meaning of O, S, or NH and n is zero to twelve.



Formula VII



Formula VII'

[0047] The compounds of formula (I) can be used as pharmaceutically active substances, especially as antimuscannic agents.

[0048] The compounds of formula (I) can be used for preparing pharmaceutical formulations containing at least one of said compounds.

II. Pharmaceutical composition of the present invention

[0049] In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

[0050] The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

[0051] The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

[0052] The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0,05 mg to about 200 g each.

III. Incubations of different compounds of the invention with human liever S 9-fraction.

[0053] A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

[0054] The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

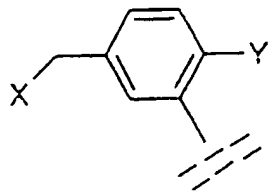
[0055] The analysis was performed by a routine High Pressure Liquid Cromatography (HPLC) method with UV-detection.

[0056] The incubation results expressed in (%) of theoretical turn-over are presented in Table 1.

[0057] They ranged from 96 to 63,2 %. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

[0058] The prodrugs introduced in the assay show the following chemical structure:

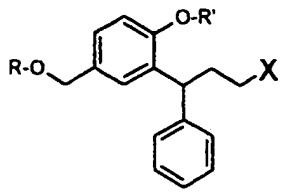


chemical structure X-/-Y

AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	butyrate
PropO-/-OProp	means	propyrate
HO-/-OProp	means	hydroxy and propyrate
HO-/-OAc	means	hydroxy and acetate

Claims

1. 3,3-Diphenylpropylamines of Formula I:



(I)

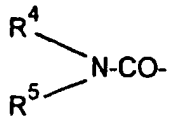
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

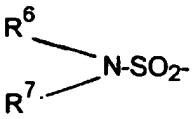
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting of



wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen;
or

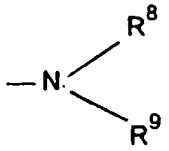
e) a group consisting of



wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

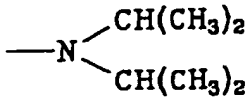
wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

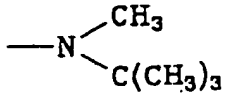
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

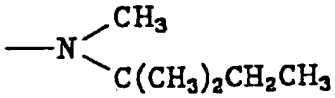
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

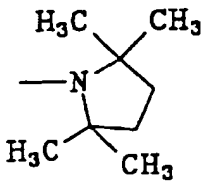
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^8 and R^9 comprises a branched carbon chain.

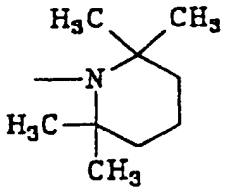
4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

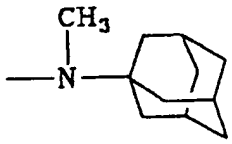
a) 

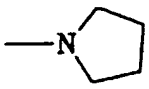
b) 

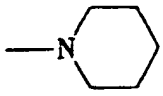
c) 

d) 

e) 

f) 

g) 

h) 

5. 3,3-diphenylpropylamines, their salts with physiologically acceptable acids, their free bases or salts thereof, racemates and individual enantiomers thereof which are definied as

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethy-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester
N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

6. 3,3-Diphenylpropylamines according to any one of claims 1 to 5 for use as pharmaceutically active substances, especially as antimuscarinic agents.

7. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1 to 6 and preferably a compatible pharmaceutical carrier.

8. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 7 for preparing an antimuscarinic drug.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 10 8608

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,D	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 * page 12, line 35 - page 13, line 15 *	1-4,6-8	C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 * abstract *	1-8	C07D207/06 C07D295/06 C07C271/08
A,D	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 * the whole document *	1,7,8	C07F7/18 C07C307/02 A61K31/135 A61K31/325 A61K31/40 A61K31/435

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07C
C07D
C07F
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	5 October 1998	Rufet, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 10 8608

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

05-10-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411337 A	26-05-1994	AT 164828 T	15-04-1998
		AU 672458 B	03-10-1996
		AU 5438094 A	08-06-1994
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		EP 0667852 A	23-08-1995
		ES 2117155 T	01-08-1998
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		AU 2932989 A	11-08-1989
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		JP 3503163 T	18-07-1991
		NO 173496 C	22-12-1993
		US 5382600 A	17-01-1995

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 019 358 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
07.05.2003 Bulletin 2003/19

(21) Application number: **98912864.0**

(22) Date of filing: **26.03.1998**

(51) Int Cl.[7]: **C07C 211/06**, C07C 215/54, C07C 217/62, C07C 237/30, C07C 255/33, C07D 333/20, A61K 31/135, A61K 31/33

(86) International application number:
PCT/SE98/00556

(87) International publication number:
WO 98/043942 (08.10.1998 Gazette 1998/40)

(54) **3,3-DIARYLPROPYLAMINES , THEIR USE AND PREPARATION**

3,3-DIARYLPROPYLAMINE , IHRE VERWENDUNG UND HERSTELLUNG

3,3-DIARYLPROPYLAMINES, LEUR UTILISATION ET LEUR PREPARATION

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **27.03.1997 SE 9701144**

(43) Date of publication of application:
19.07.2000 Bulletin 2000/29

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(56) References cited:
WO-A-89/06644
WO-A-94/11337
DE-B- 1 216 318
GB-A- 1 169 944
GB-A- 1 169 945

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Printed by Jouve, 75001 PARIS (FR)

EP 1 019 358 B1

Description

TECHNICAL FIELD

[0001] The present invention relates to novel therapeutically active compounds, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

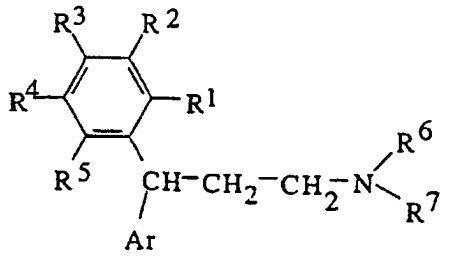
BACKGROUND OF THE INVENTION

[0002] WO 89/06644 and WO 94/11337 disclose tertiary 3,3-diphenylpropylamines having anticholinergic activity, especially for the treatment of urinary incontinence. SE-A-215499 discloses secondary 3,3-diphenylpropylamines having an advantageous effect on the heart and circulation. US-A-3,446,901, GB-A-1,169,944 and GB-A-1,169,945 disclose 3,3-diphenylpropylamines having antidepressant activity. DE-B1-1216318 discloses preparation of diphenylalkylamines having effect on the heart and circulation.

SUMMARY OF THE INVENTION

[0003] In accordance with the present invention, novel therapeutically active diarylpropylamines have been found which like the 3,3-diphenylpropylamines known from WO 89/06644 and WO 94/11337 above have favourable anticholinergic properties, and which therefore also can be used for the control of events mediated by acetylcholine, like urination.

[0004] In one aspect, the present invention provides novel compounds represented by the general formula I:



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,

R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl of at least two carbon atoms, alkoxy of at least two carbon atoms, hydroxyalkyl of at least two carbon atoms,

R^5 is hydrogen, halogen, alkyl,

Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and

R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen,

with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or

(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or

(iii) Ar is heteroaryl, or

(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then

R^4 may also be hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, halogen, carbamoyl, sulphamoyl;
and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;
their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

[0005] In another aspect, the present invention provides the compounds having the general Formula I above for therapeutical use, especially for the treatment of urinary incontinence related disorders.

[0006] In still another aspect, the present invention provides a pharmaceutical composition comprising one or more compounds of the general Formula I above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

[0007] In yet another aspect, the present invention provides a method of treating a patient (animals, including humans) suffering from a disorder related to urinary incontinence, which method comprises the step of administering to the said patient an effective amount of a compound having the general Formula I above.

[0008] In another aspect, the present invention provides the compounds according to Formula I for use as a pharmaceutically active substance, especially as an anticholinergic agent.

[0009] In yet another aspect, the present invention provides the use of the compounds having the general Formula I above for the manufacture of a medicament for the treatment of urinary incontinence related disorders.

[0010] In still another aspect, the present invention provides processes for preparing compounds having the general Formula I above.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The present invention comprises novel 3,3-diarylpropylamines and their pharmaceutically acceptable salts which are characterized by Formula I above and which are useful as anticholinergic agents. The compounds are particularly useful for treatment of urinary incontinence.

[0012] One subgroup of compounds of Formula I is defined by the substituent R^4 being ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

[0013] In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

[0014] Another subgroup of the compounds of Formula I is defined by Ar being heteroaryl.

[0015] In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

[0016] Still another subgroup of the compounds of Formula I is defined by R^1 being hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen. Preferaby, Ar is then other than phenyl that is ortho-substituted by hydroxy or alkoxy.

[0017] In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

[0018] Yet another subgroup of the compounds of Formula I is defined by at least one of R^6 and R^7 being aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom at one or more positions.

[0019] In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

[0020] In the compounds of Formula I, "alkyl", separately and in combinations, is preferably C_{1-8}alkyl, i.e. methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof, more preferably C_{1-6}alkyl, especially C_{1-4}alkyl.

[0021] Similarly, "alkoxy", separately and in combinations, is preferably C_{1-8}alkoxy, i.e. methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy, and isomeric forms thereof, more preferably C_{1-6}alkoxy, especially C_{1-4}alkoxy.

[0022] "Aryl" means phenyl or naphthyl. "Heteroaryl" refers to a 5- or 6-membered heteroaromatic ring having from one to three heteroatoms, and which optionally may be fused to a homoaromatic ring, such as a benzene ring. Exemplary heteroaryl groups are morpholinyl, thienyl, furyl, piperazinyl, piperidinyl, imidazolinyl, pyridazolinyl, oxazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl.

[0023] "Halogen" includes fluoro, chloro, bromo and iodo.

[0024] When aryl is mono-substituted, it is preferably substituted in 2-position. When aryl is di-substituted, it is preferably substitued in positions 2 and 4. Preferred substituents are methyl, methoxy, hydroxy, hydroxymethyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, especially methyl, hydroxymethyl and halogen. Aryl is preferably phenyl.

[0025] Preferred heteroaryl groups are thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl and methylpyrryl.

[0026] R^1 is preferably hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

[0027] R^2 and R^3 are preferably selected from hydrogen, hydroxy and methoxy.

[0028] R^4 is preferably hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyl, amino, azido, cyanoalkyl, carboxy or carboxyalkyl. More preferably, R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethylaminoethyl.

[0029] R^5 is preferably hydrogen.

[0030] R^6 and R^7 independently of each other preferably signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group, such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms. R^6 and R^7 may carry one or more hydroxy groups and they may be joined to form a ring together with the nitrogen atom. It is preferred that at least one of R^6 and R^7 comprises a branched carbon chain.

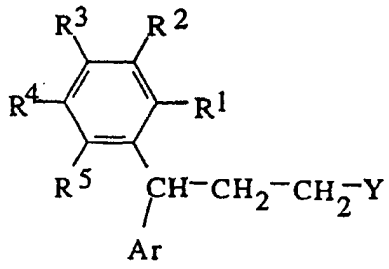
[0031] Exemplary groups $-NR^6,R^7$ are diethylamino, diisopropylamino, methyl-tert.-butylamino, methyl-tert.-pentylamino, piperidino, 2,2,6,6-tetramethylpiperidino, methylcyclobutylamino, methylcyclopentylamino, methylcyclohexylamino, methylcycloheptylamino, pyrrolidino, 2,2,5,5-tetramethylpyrrolidino, N-methyl-N-adamantylamino, especially diisopropylamino.

[0032] Representative compounds of Formula I are:

N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine, and its 3(R)-isomer
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its 1(S*)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, and its (R)-isomer

[0033] The compounds of Formula I may, in accordance with the present invention, be prepared by per se conventional methods, and especially by

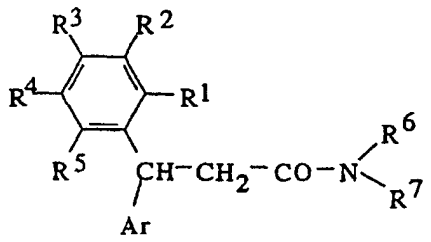
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined above for Formula I, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

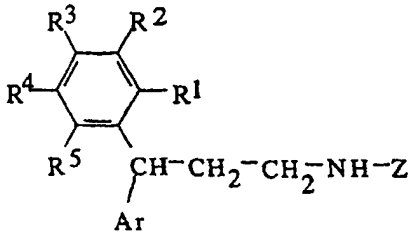
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, or

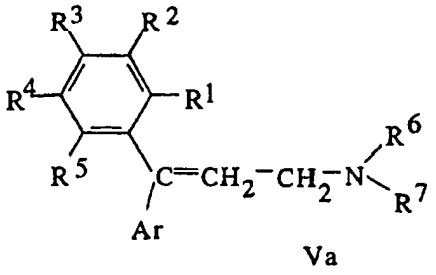
c) N-alkylating a secondary amine of Formula IV



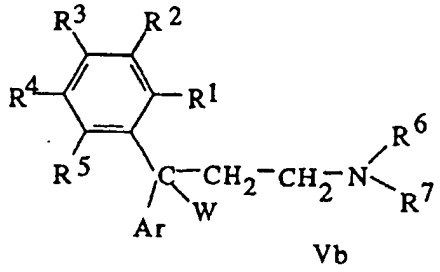
IV

wherein R^1 to R^5 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



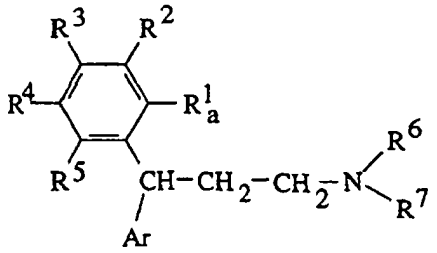
Va



Vb

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

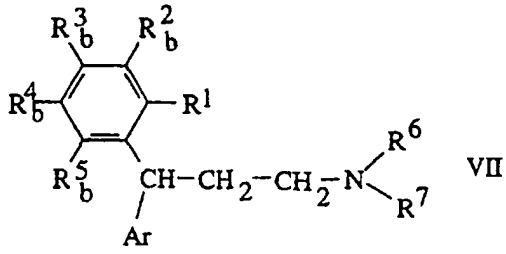
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined above for Formula I, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

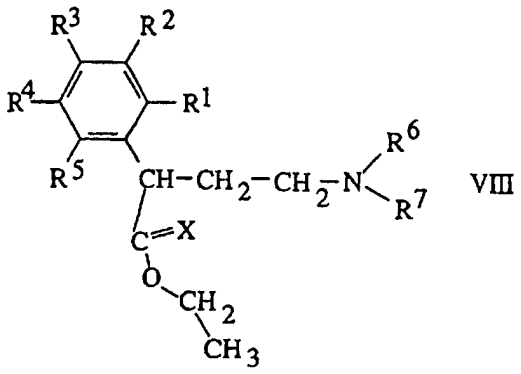


VII

wherein R^1, R^6, R^7 and Ar are as defined above for Formula I, and one of R^2b to R^5b is alkylene and the others are as defined above for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined above, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

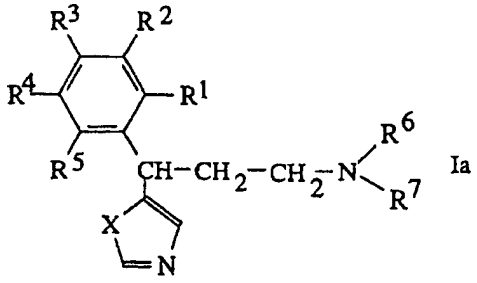


VIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, with a compound of Formula IX

$$CH_3N{=}C: \qquad \text{IX}$$

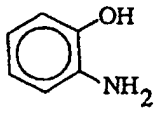
to form a compound of Formula Ia



Ia

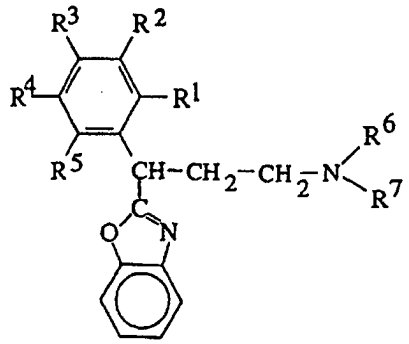
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

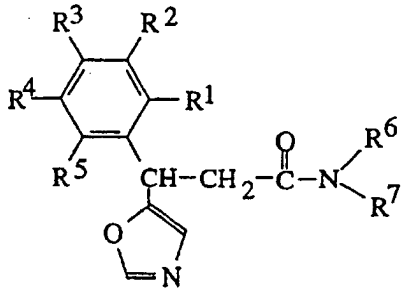
to form a compound of Formula Ib



Ib

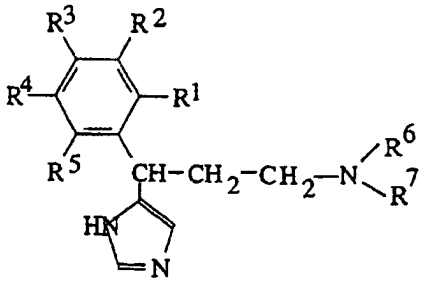
wherein R^1 to R^7 are as defined above for Formula I, or

j) converting a compound of Formula XI



XI

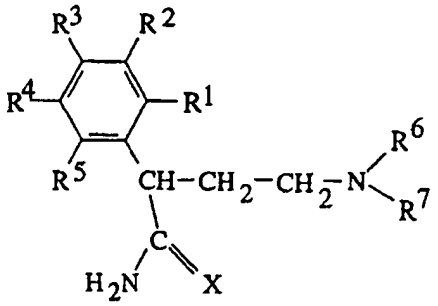
wherein R^1 to R^7 are as defined above for Formula I, to a compound of Formula XII



XII

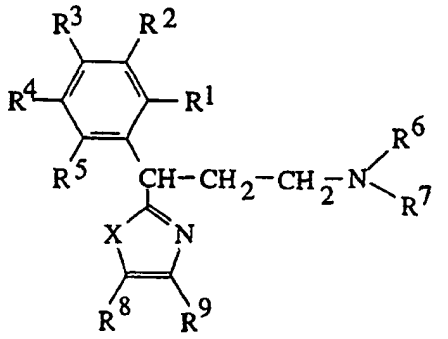
wherein R^1 to R^7 are as defined above for Formula I, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, to a compound of Formula XIV



XIV

wherein R^1 to R^7 and X are as defined above for Formula I, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,
ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

[0034] Appropriate reaction conditions in the above reactions may readily be selected by the skilled person with reference to analogous prior art methods and with due consideration of the specific Examples below. The necessary starting materials are either known or may be prepared in analogy with the preparation of known compounds.

[0035] The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e. g. be achieved by fractional crystallisation of salts with chiral acids or by chromatographic separation on chiral columns.

[0036] In accordance with the present invention, the compounds of Formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of Formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

[0037] The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

[0038] The compounds and compositions can, as mentioned above, be used for the same therapeutical indications as the compounds of the above-mentioned WO 89/06644 or WO 94/11337, i.e. for the treatment of acetylcholine-mediated disorders, such as urinary incontinence, especially urge incontinence. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of

the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kilo of body weight, administered singly or multiply in doses e.g. from about 0,05 mg to about 200 mg each.

[0039] The invention will be further illustrated by the following non-limiting example and pharmacological tests.

General

[0040] N.M.R data were acquired on a Jeol JNM-EX 270 or a Varian Unity 500 spectrometer. Spectra were recorded with tetramethylsilane (TMS) as internal standard at 30°C. Infrared spectra were recorded on a Perkin-Elmer Model Model 841 spectrophotometer. Non-corrected melting points were obtained on a Koeffler apparatus. Gas chromatography was performed on a HP 5940 instrument with a 10 m HP-1 column and the oven heated in the linear temperature gradient mode. All lithium aluminum hydride reductions were quenched by the use of the procedure according to V. Micovic and M. Mihailovic (J. Org. Chem. 18, 1190 (1953)).

EXAMPLE 1

N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

[0041] A solution of N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (2.75 g, 7 mmol) in THF (40 mL) was added to lithium aluminum hydride (LAH) (0.50 g, 13 mmol) and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 19:1). The title compound was crystallised by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.75 g (27%); mp 70-75°C. ^{1}H NMR (DMSO-d6) δ 1.17 (q, 3H), 1.23 (t, 3H), 2.18 (d, 3H), 2.47 (m, 2H), 2.84-3.07 (m, 2H), 3.15 (m, 1H), 3.37 (m, 1H), 3.42 (d, 2H), 3.46 (s, 2H), 3.67 (m, 1H), 3.74 (m, 2H), 4.30 (m, 1H), 4.76 (br, 1H), 6.71 (d, 1H), 6.80 (d, 1H), 7.06 (d, 1H), 7.16 (t, 1H), 7.27 (t, 2H), 7.33 (d, 2H), 9.29 (d, 1H) and 10.07 (br, 1H). Anal. ($C_{23}H_{33}NO_3$·HCl) C, H, N.

[0042] The starting compound N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

1.1 Trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid

[0043] A solution of triethyl phosphonoacetate (22.4 g, 0.10 mol) in THF (150 mL) was added to sodium hydride (80%, 2.7 g, 0.09 mol) under nitrogen during 15 min. The resulting mixture was refluxed for 15 min whereafter a solution of 2-benzyloxy-5-methyl-benzophenone (15.1 g, 0.05 mol) in THF (50 mL) was added. The reaction mixture was refluxed for 19 h. Water and sodium hydroxide (10 g, 0.25 mol) were added and most of the THF was distilled off. Ethanol was added until a clear solution was obtained and the reflux was continued for a few minutes. Water was added to a total volume of 1 L and the mixture was washed with diethyl ether. Hydrochloric acid was added to the water-phase and a crystalline mass was obtained. The pure trans-isomer was obtained by recrystallisation from ethanol. Yield 10.4 g (60%). ^{1}H NMR (DMSO-d6) δ 2.24 (s, 3H), 4.92 (s, 2H), 6.41 (s, 1H), 6.87 (d, 1H), 6.98 (d, 1H), 7.03 (m, 2H) 7.12 (m, 1H), 7.22 (m, 3H), 7.29 (m, 1H), 7,30 (m, 1H) and 7.33-7.39 (m, 3H).

1.2 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0044] A solution of DCC (5.2 g, 17 mmol) in THF (20 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (6.9 g, 20 mmol), 2-(2-isopropylaminoethoxy)-ethanol, triethylamine (2.5 g, 25 mmol) and hydroxysuccinimide (2.8 g, 24 mmol) in THF (50 mL). The reaction mixture was stirred for 20 h. The solvent was evaporated and the residue chromatographed on silica (gradient from toluene to ethyl acetate). Yield 5.9 g (62%).

1.3 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

[0045] A solution of trans-N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3- (2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (5.9 g, 12 mmol) in acetic acid (50 mL) was hydrogenatated over Pd/C (10 %, 0.5 g) for 16 h. Filtering and evaporation of solvent left a residue that was chromatographed on silica (ethyl acetate). Yield 2.83 g (61 %).

EXAMPLE 2

N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

[0046] A solution of N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (0.93 g, 2.5 mmol)

in THF (20 mL) was added to LAH (0.22 g, 5.6 mmol) and the mixture was stirred at reflux temperature for 30 min. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (chloroform-methanol 9:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.45 g (46%); mp. 230-232°C. ^{1}H NMR (DMSO-d6) δ 1.27-1.70 (m, 10H), 1.88 (br, 1H), 2.05 (d, 1H), 2.17 (s, 3H), 2.42 (br, 1H), 2.60 (s, 3H), 2.85 (br, 2H), 3.34 (m, 1H), 4.30 (t, 1H), 6.72 (d, 1H), 6.80 (dd, 1H), 7.05 (br, 1H), 7.15 (t, 1H), 7.27 (t, 2H), 7.31 (d, 2H), 9.31 (s, 1H) and 10.53 (br, 1H). Anal. ($C_{24}H_{33}NO$·HCl) C, H, N.

[0047] The starting compound N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

2.1 N-Cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0048] A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g, 20 mmol), cycloheptylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at room temperature. Another portion of cycloheptylamine (1.3 g) was added and the reaction mixture was left stirring for another 1 h. The mixture was filtered and the filtrate evaporated. The residue was dissolved in diethyl ether and washed with hydrochloric acid (1M), water and brine in subsequent order. After evaporation of the solvent, the residue was crystallised from toluene-hexane to give 7.3 g (83%). ^{1}H NMR ($CDCl_3$) δ 1.06 (br, 2H), 1.25-1.74 (m, 10H), 2.30 (s, 3H), 3.83 (m, 1H), 4.95 (s, 2H), 5.50 (d, 1H), 6.49 (s, 1H), 6.90-7.08 (m, 4H), and 7.12-7.44 (m, 9H).

2.2 N-Cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0049] A solution of N-cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.4 g, 10 mmol) and methyliodide (4 g, 30 mmol) in DMF (10 mL) was added to sodiumhydride (80 %, 1.2 g, 40 mmol) at ambient temperature and the mixture was stirred for 60 min. Excess sodium hydride was destroyed by adding methanol, and the reaction mixture was then partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallised from toluene-hexane to yield 4.4 g (97%). ^{1}H NMR ($CDCl_3$) (almost 1:1 mixture of rotameres) δ 1.20-1.80 (m, 12H), 2.30 (m, 3H) 2.61 (s, 1.5H), 2.71 (s, 1.5H), 3.93 (m, 0.5H), 4.46 (m, 0.5H), 4.81 (m, 1H), 6.43 (m, 1H), 6.81 (m, 2H) and 7.08-7.35 (m, 10H).

2.3 N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

[0050] A solution of N-cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (3.15 g, 7 mmol) in acetic acid (40 mL) was hydrogenated over Pd/C (10%, 0.2 g) for 72 h. The reaction mixture was filtered and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 0.95 g (37%). ^{1}H NMR ($CDCl_3$) δ 1.26-1.98 (m, 12H), 2.02 (s, 3H), 2.12 (s, 3H), 2.28 (m, 1H), 2.52 (m, 1H), 2.71 (m, 1H), 4.36 (dd, 1H), 6.39 (s, 1H), 6.76 (s, 2H), 7.15 (m, 2H) and 7.25 (m, 5H).

EXAMPLE 3

N-Cyclohexyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

[0051] A solution of N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.0 g, 9 mmol) in THF (90 mL) was added to LAH (0.50 g, 13 mmol) in THF (5 mL) and the mixture was stirred at ambient temperature for 2.5 h. The reaction was quenched and the solvent evaporated. The resulting oil was hydrogenated over Pd/C (10%, 1g) in acetic acid (70 mL) for 20 h. After filtration and evaporation of the solvent, the residue was chromatographed on silica (chloroform:methanol 99:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 1.2 g (36%); mp. 179-183°C. ^{1}H NMR (DMSO-d6) δ 1.05 (m, 1H), 1.21-1.38 (m, 4H), 1.51 (d, 1H), 1.74 (br, 2H), 1.86 (br, 1H), 2.00 (d, 1H), 2.17 and 2.19 (s, 3H), 2.39-2.56 (m, 2H), 2.63 (m, 3H), 2.82 (m, 1H), 2.93 (m, 1H), 3.17 (m, 1H), 4.32 (q, 1H), 6.73 and 6.75 (d, 1H), 6.79 and 6.81 (t, 1H), 7.02 and 7.10 (d, 1H), 7.14-7.18 (m, 1H), 7.25-7.29 (m, 2H), 7.33 (t, 2H), 9.34 (br, 1H) and 10.78 (s, 1H). Anal. ($C_{23}H_{31}NO$·HCl) C, H, N.

[0052] The starting compound N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl) -3-phenylpropenamide was prepared as follows:

3.1 N-Cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0053] A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-meth-

ylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g, 20 mmol), N-methyl-cyclohexylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 2 h. A second portion of DCC (2.5 g, 13 mmol) and N-methyl-cyclohexylamine (1.5 g, 13 mmol) was added and the reaction mixture was left stirring for 16 h. Diethyl ether and hydrochloric acid (1M) were added and the organic phase was washed with brine. The organic layer was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 5.5 g (63%). ^{1}H NMR (DMSO-d6) (almost 1:1 mixture of rotameres) δ 0.88-1.06 (m, 2H), 1.16-1.39 (m, 5H), 1.55 (t, 2H), 1.67 (br, 1H), 2.21 (s, 1.5H), 2.23 (s, 1.5H) 2.56 (s, 1.5H), 2.67 (s, 1.5H), 3.67 (m, 0.5H), 4.05 (m, 0.5H), 4.82 (s, 1H), 4.85 (s, 1H), 6.57 (s, 0.5H), 6.59 (s, 0.5H), 6.84 (dd, 1H), 6.87 (d, 0.5H), 6.89 (t, 1H), 6.95 (dd, 1H), 6.98 (d, 0.5H), 7.12 (dd, 1H), 7.17 (m, 3H), 7.27 (m, 2H), and 7.32 (m, 3H).

EXAMPLE 4

N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamine hydrochloride

[0054] Boran·SMe_2-complex in THF (7 mL, 14 mmol) was gently refluxed with a weak stream of nitrogen for 30 minutes. N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide (1.55 g, 4.2 mmol) was added to the refluxing solution and the reflux was continued for 1 h. The reaction mixture was partioned between diethyl ether and sodium hydroxide (1M). The solvent of organic layer was evaporated and the residue was chromatographed on silica (toluene-triethylamine 9:1) to yield the free amine. The hydrochloride salt was obtained by dissolving the amine in diethyl ether with the addition of hydrogen chloride in diethyl ether. The resulting oil produced crystals after some time stirring in diethyl ether. Yield 0.39 g (23%); mp. 143-144°C. ^{1}H NMR (DMSO-d6) δ 1.19 (q, 6H), 1.25 (dd, 6H), 2.53 (m, 1H), 2.70 (m, 1H), 2.87 (m, 2H), 3.59 (m, 2H), 4.38 (t, 1H), 7.24 (t, 1H), 7.35 (t, 2H), 7.39 (d, 2H), 7,45 (t, 1H), 7.68 (t, 1H), 7.74 (t, 2H) and 10.25 (br, 1H). Anal. ($C_{22}H_{28}NF_3$·HCl) C, H, N.

[0055] The starting compound N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide was prepared as follows:

4.1 Diethyl N,N-diisopropylacetamide phosphonate

[0056] A mixture of triethylphosphite (23 g, 0.14 mol) and N,N-diisopropyl 2-bromoacetamide (29 g, 0.13 mol) was heated to 110°C for 3 h to yield 35 g (97%). The product was used without purification.

4.2 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide

[0057] A solution of diethyl N,N-diisopropylacetamide phosphonate (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 29 mmol) during 30 min, keeping the temperature below 30°C. A solution of 2-trifluoromethyl-benzophenone (5.0 g, 20 mmol) in THF (20 mL) was added and the reaction mixture was heated to 50°C and kept at that temperature for 16 h. A second portion of the phosphorous ylide (15 mmol), prepared as above, was added. After another 24 h at 50°C the mixture was partioned between diethyl ether and water. The etheral layer was evaporated and the residue chromatographed on silica (toluene-ethyl acetate 9:1) yielding 3.0 g (41%) as a mixture of the E- and Z-isomers. Labels a and b refer to the different isomers. ^{1}H NMR ($CDCl_3$-d) δ 0.80 (d, 6Ha), 1.08 (d, 3Hb), 1.24 (t, 6Hb), 1.31 (d, 3Hb), 1.44 (d, 6Ha), 3.32 (m, 1Ha), 3.34 (m, 1Hb), 4.19 (m, 1Hb), 4.32 (m, 1Ha), 6.04 (s, 1Ha), 6.65 (s, 1Hb) and 7.18-7.75 (m, 9Ha, 9Hb).

4.3 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide

[0058] A solution of N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide (2.95 g, 8.1 mmol) in ethanol (50 mL) was hydrogenated over Pd/C (10%, 300 mg) at normal pressure for 24 h. The catalyst was filtered off, the solvent partly evaporated and the product collected after crystallisation. Yield 1.78 g (60%). ^{1}H NMR ($CDCl_3$-d) δ 1.16 (m, 6H), 1.30 (m, 6H), 2.86 (dd, 1H), 3.11 (dd, 1H), 3.41 (m, 1H), 4.03 (m, 1H), 5.12 (m, 1H) and 7.10-7.78 (m, 9H).

EXAMPLE 5

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(3-pyridyl)-propanamine dihydrochloride

[0059] A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide (2.8 g, 8 mmol) in THF (25 mL) was added to LAH (1.3 g, 32 mmol). The reaction mixture was refluxed for 4 h whereafter the reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 99:1) to give 2.2 g. The product (1.3 g, 4 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to -78°C and boron

tribromide (1 g, 8 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature during 1 h. The reaction mixture was washed with sodium hydroxide (1M) and brine and the organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 9:1) to give 0.35 g. The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to produce the dihydrochloride as crystals which soon rearranged to a hard glass. ^{1}H NMR (DMSO-d6) δ 1.22 (dd, 6H), 1.28 (dd, 6H), 2.60 (m, 1H), 2.70 (m, 1H), 2.93 (m, 2H), 3.60 (m, 2H), 4.60 (t, 1H), 6.85 (t, 1H), 6.89 (d, 1), 7.11 (t, 1H), 7.38 (d, 1H), 7.96 (dd, 1H), 8.46 (d, 1H), 8.75 (d, 1H), 8.85 (s, 1H), 9.90 (br, 1H) and 10.14 (s, 1H).

[0060] The starting compound N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide was prepared as follows:

5.1 2-Methoxyphenyl-3-pyridyl-ketone

[0061] A solution of 2-bromoanisole (21 g, 0.11 mol) in diethyl ether (100 mL) was added to magnesium turnings during 45 minutes with heating. After the addition the reflux was continued for 15 min. The Grignard reagent was cooled to 0°C and a solution of 3-cyanopyridine (10 g, 0.10 mol) in diethyl ether (100 mL) was added dropwise. The mixture was refluxed for a few minutes. Hydrochloric acid (20 mL, 0.24 mol, conc.) and 2-propanol (20 mL) were added and the reflux was continued for 30 min. Water and diethyl ether were added and the phases separated. The water-phase was made alkaline (2M NaOH) and was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated to yield 17 g. The crude was chromatographed on silica (toluene-ethyl acetate 19:1) to give 3.75 g (19%). ^{1}H NMR ($CDCl_3$-d) δ 3.76 (s, 3H), 7.01 (d, 1H), 7.10 (t, 1H), 7.41 (dd, 1H), 7.46 (dd, 1H), 4.53 (m, 1H), 8.12 (d, 1H), 8.75 (s, 1H) and 8.94 (s,

5.2 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide

[0062] A solution of of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (9.3 g, 33 mmol) in THF (40 mL) was added dropwise to sodium hydride (80 %, 1.0 g, 33 mmol) during 15 min. The mixture was heated to 40°C for 15 minutes and then cooled to 5°C whereafter a solution of 2-methoxyphenyl-3-pyridyl-ketone (4.5 g, 21 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 16 h. The reaction mixture was partioned between diethyl ether and water and the organic phase was dried ($MgSO_4$) and evaporated to yield 7.1 g of solid material. The product was hydrogenated over Pd/C (10%, 0.2 g) in acetic acid (50 mL) for 48 h. The reaction mixture was filtered and the solvent evaporated. The residue was partioned between diethyl ether and hydrochloric acid (1 M) and the phases were separated. The water-phase was made alkaline (2 M sodium hydroxide) and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and filtered. Crystallisation began and the mixture was diluted with hexane. Filtration gave 2.9 g (40%). ^{1}H NMR ($CDCl_3$-d) δ 1.14 (dd, 6H), 1.28 (d, 6H), 3.04 (dd, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.05 (m, 1H), 5.00 (t, 1H), 6.84 (d, 1H), 6.92 (t, 1H), 7.19 (m, 3H), 7.57 (d, 1H), 8.39 (m, 1 H) and 8.55 (d, 1H). 1H).

EXAMPLE 6

N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

[0063] A solution of N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide (3.1 g, 9.4 mmol) in THF (20 mL) was added to LAH (1.0 g, 25 mmol) and the reaction mixture was stirred at reflux temperature for 2 h. More LAH (0.5 g), was added and the reflux continued for another 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 3:1) to give 0.4 g of the free amine as a syrup. The amine was dissolved in isopropanol/diethyl ether and hydrogen chloride in diethyl ether was added to give the amine salt. Yield 0.32 g (10 %); mp 152-154 °C. ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.26 (dd, 6H), 2.57 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.36 (t, 1H), 6.69 (dd, 1H), 7.14 (m, 1H), 7.22 (m, 2H), 7.29 (m, 1H), 7.32 (d, 2H), 7.33 (s, 2H), 7.54 (m, 1H) and 10.24 (br, 1H). Anal. ($C_{21}H_{28}NF$·HCl) H, N; C: calcd, 72.1; found, 72.6.

[0064] The starting compound N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide was prepared as follows:

6.1 trans-N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide

[0065] A solution of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 25 mmol) during 30 min, keeping the temperature below 40°C. A solution of 2-trifluoromethyl-benzophenone (4.0 g, 20 mmol) in THF (10 mL) was added and the reaction mixture was stirred at ambient temperature for 30 min. The mixture was partioned between diethyl ether and brine. The organic layer was dried ($MgSO_4$) and evaporated to give a crystalline mass. Recrystallisation from hexane yielded 3.9 g (60

%). ^{1}H NMR ($CDCl_3$-d) δ 0.85 (d, 6H), 1.39 (d, 6H), 3.29 (m, 1H), 4.27 (m, 1H), 6.29 (s, 1H), 7.10 (m, 3H) and 7.30 (m, 6H).

6.2 N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide

[0066] A solution of trans-N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide (3.25 g, 10 mmol) was hydrogenated over Pd/C (10%, 300 mg) in acetic acid (30 mL) for 24 h. The catalyst was filtered off and the solvent was evaporated to yield 3.15 g (96%). ^{1}H NMR ($CDCl_3$-d) δ 1.12 (q, 6H), 1.28 (q, 6H), 3.05 (d, 2H), 3.38 (m, 1H), 4.03 (m, 1H), 4.93 (t, 1H) and 6.94-7.32 (m, 9H).

EXAMPLE 7

(R) -N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0067] Hydrogen chloride in diethyl ether was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (0.81 g, 2.4 mmol) in diethyl ether and 2-propanol. Crystals were filtered to yield 0.4 g (45%); mp 178-179°C. $[\alpha]_{Hg}$ = -40° (c 1.1 in methanol) . ^{1}H NMR (DMSO-d6) δ 1.16 (d, 3H), 1.20 (d, 3H), 1.24 (d, 3H), 1.27 (d, 3H), 2.54 (m, 2H), 2.84 (m, 1H), 2.97 (m, 1H), 3.58 (br, 2H), 4.38 (t, 1H), 7.08 (d, 1H), 7.22 (t, 1H), 7.32 (m,4H), 7.65 (dd, 1H), 7.83 (d, 1H), 9.80 (s, 1H), 9.86 (br, 1H) 10.99 (s, 1H). Anal. ($C_{22}H_{29}NO_2$·HCl) H, N; C: calcd, 70.3; found, 70.8.

[0068] The starting compound (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine was prepared as follows:

7.1 (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine

[0069] DDQ (1.1 eq) was added to a solution of (R)-N,N-diisopropyl-3- (2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine mandelate (prepared as described in WO 94/11337, Example 1) (2.46 g, 5 mmol), dichloromethane (20 mL) and phosphate buffer (pH 7) (0.1 mL). Thereafter, sodium hydroxide solution (20 mL, 1 M) and diethyl ether were added and the phases were separated. The water-phase was extracted twice with dichloromethane-diethyl ether (2:1). The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate-hexane to yield 1.35 g (80 %).

EXAMPLE 8

(R)-N,N-Diisopropyl-3-[5-(7-hydroxy-2-aza-5-oxaheptyl)-2-hydroxyphenyl]-3-phenylpropanamine di-(S)-mandelate

[0070] Sodiumcyanoborohydride (0.25 g, 3.9 mmol) was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (Example 7.1), (1.25 g, 3.7 mmol) and 2-ethoxy-(2-amino)-ethanol (19.5 g, 18 mmol) in methanol (10 mL). Hydrochloric acid (conc) was added to adjust pH to about 3. After 3h, the pH was adjusted to about 1 and the solvent was evaporated. The residue was partioned between diethyl ether and water, whereafter the organic layer was evaporated and the residue chromatographed on silica (chloroform-triethylamine-methanol 88: 10:2). The pure amine was dissolved in 2-propanol-diethyl ether with (S)-mandelic acid (2 eq), whereby the product crystallised (the crystals were unstable and an oily mass was soon obtained). Yield 0.2 g (7%); mp dec. ^{1}H NMR (free amine) ($CDCl_3$-d) δ 1.05 (d, 6H), 1.09 (d, 6H), 2.10 (m, 1H), 2.35 (m, 2H), 2.67 (m, 3H), 3.19 (m, 2H), 3.47 (m, 2H), 3.49 (t, 2H), 3.56 (d, 2H), 3.63 (t, 2H), 4.45 (dd, 1H), 6.75 (d, 1H), 6.79 (d, 1H), 6.95 (dd, 1H), 7.18 (m, 1H) and 7.26-7.33 (m, 4H).

EXAMPLE 9

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine hydrochloride

[0071] A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (0.92 g, 2 mmol) in ethanol (30 mL) was hydrogenated over Pd/C (10%, 50 mg) at room temperature for 2 h. The catalyst was filtered off and the solution was treated with hydrogen chloride to obtain the amine salt. Yield 0.66 g (81 %); mp 177-178°C; $[\alpha]_D$ = -23° (c 1.0, methanol). ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.25 (dd, 6H), 2.48 (m, 2H), 2.85 (m, 1H), 2.95 (m, 1H), 3.58 (m, 2H), 3.78 (s, 3H), 4.38 (t, 1H), 6.98 (d, 1H), 7.20 (m, 1H), 7.31 (d, 2H), 7,32 (s, 2H), 7.69 (dd, 1H), 7.81 (d, 1H), 9.85 (br, 1H), 10.74 (s, 1H). Anal.

($C_{23}H_{31}NO_3$·HCl) H, N, C.

EXAMPLE 10

N,N-Diisopropyl-3-(2-hydroxymethyl)phenyl-3-phenylpropanamine hydrochloride

[0072] A solution of N,N-diisopropyl-3-(2-carboxyphenyl)-3-phenylpropanamine hydrochloride (1.88 g, 5 mmol) in THF (30 mL) was added to LAH (1.5 g, 38 mmol) and the reaction mixture was stirred att ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was dissolved in hot diethyl ether-2-propanol (100 mL, 1:4), whereafter HCl in diethyl ether was added. After cooling the product was filtered and dried at 60°C (vacuum). Yield 1.2 g (68%); mp 223-224°C. ^{1}H NMR (DMSO-d6) δ 1.18 (t, 6H), 1.25 (q, 6H), 2.91 (m, 2H), 3.26 (disturbed by solvent, 2H), 3.57 (m, 2H), 4.38 (t, 1H), 4.43 (d, 1H), 4.74 (d, 1H), 5.22 (s, 1H), 7.20 (q, 2H), 7.25-7.35 (m, 5H), 7.40 (dd, 2H), 9.95 (s, 1H). Anal. ($C_{22}H_{31}NO$·HCl) H, N, C.

EXAMPLE 11

(S)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

[0073] (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (0.67 g, 1.5 mmol) was hydrogenated over Pd/C (10%, 67 mg) at atmospheric pressure overnight in ethanol (20 mL). The catalyst was filtered off and the solvent was evaporated. The residue was partioned between diethyl ether and sodium hydroxide (1 M). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The amine salt was obtained by dissolving the amine in diethyl ether-isopropanol and treatment with hydrogen chloride in diethyleter. Yield 0.37 g; mp 219-221 °C; $[\alpha]_D$ -11.4° (c=1.0, methanol); ^{1}H NMR (CD_3OD) δ 1.30 (d, 12H), 2.36-2.60 (m, 2H), 2.68 (t, 2H), 3.05 (t, 2H), 3.60-3.72 (m, 4H), 4.40 (t, 1H), 6.73 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.17-7.38 (m, 5H). Anal. ($C_{23}H_{33}NO_2$·HCl·0.2H_2O) C, H, N.

[0074] The starting compound (S)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxy)ethylphenyl]-3-phenylpropanamine was prepared as follows:

11.1 (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

[0075] A mixture of (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8 g, 12.7 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), tri-o-tolyl-phosphine (74 mg, 0.14 mmol) and tributylamine (5.9 mL, 24.5 mmol) in dimethylacetamide (50 mL) was heated to 60 °C under nitrogen atmosphere. Ethene (g) was then added to 8 bars pressure. After stirring overnight the reaction mixture was allowed to cool to room temperature. Nitrogen was flushed through the reaction vessel, and toluene and water were added. The aqueous layer was extracted with toluene and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was treated with sodium hydroxide (1 M) and extracted with diethyl ether and toluene. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica (gradient ethyl acetate-methanol 90:10 up to 0.06% NH_3 in ethyl acetate-methanol 90:10) Yield 1 g (18%); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

11.2 (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0076] (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (1 g, 2.34 mmol) in THF (25 mL) was added to 9-BBN (0.5 M in THF, 11.7 mL, 5.85 mmol) under nitrogen atmosphere at 0 °C. Additional 9-BBN (2.3 mL, 1.2 mmol) was added after 3 hours of stirring, the temperature was raised to room temperature and the mixture was stirred for 0.5 hour. It was then cooled to 0 °C and 1 M sodium hydroxide (10 mL) was added followed by H_2O_2 (30% in H_2O, 10 mL). After 1 hours stirring, water was added and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (gradient of diethyl ether to 1% NH_3 in diethyl ether). Yield 0.67 g (64%). ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 12H), 2.10-2.18 (m, 2H), 2.30-2.37 (m, 2H), 2.80 (t, 2H), 2.90-3.0 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 5.0 (s, 2H), 6.80 (d, 1H), 7.0 (m, 1H), 7.10-7.38 (m, 11H).

EXAMPLE 12

(R)-N,N-Diisopropyl-3- [2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

[0077] The title compound as well as the starting compounds were prepared in an analogous manner to the preparation described in Example 11, with the exception that (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was changed to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1).

Yield 0.35 g (33%); mp 209-215 °C; $[\alpha]_D$ +9.8° (c=1.0, methanol); ^{1}H NMR (CD_3OD) δ 1.29 (d, 12H), 2.40-2.60 (m, 2H), 2.67 (t, 2H), 3.04 (t, 2H), 3.61-3.72 (m, 4H), 4.40 (t, 1H), 6.70 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.18-7.40 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

[0078] Preparation of starting compounds:

12.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

[0079] Yield 5.5 g (53%); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

12.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0080] Yield 1.2 g (75%); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 12H), 2.15 (m, 2H), 2.32 (m, 2H), 2.80 (t, 2H), 2.95 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 4.98 (s, 2H), 6.80 (d, 1H), 6.96 (m, 1H), 7.10-7.35 (m, 11H).

EXAMPLE 13

(R)-N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0081] (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine (1 g, 2.25 mmol) was treated as described in Example 11. Yield 0.6 g (68%); mp 105-115 °C; $[\alpha]_D$ -32.6° (c 1.02, methanol); ^{1}H NMR (DMSO-d_6) d 1.18-1.28 (m, 12H), 2.5 (m, 3H), 2.50-2.62 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.38 (t, 1H), 6.99 (d, 1H), 7.2 (m, 1H), 7.29-7.35 (m, 4H), 7.73 (dd, 1H), 7.85 (d, 1H), 9.90 (br, 1H), 10.70 (s, 1H). Anal. ($C_{23}H_{31}NO_2 \cdot HCl \cdot 0.4H_2O$) C, H, N.

[0082] The starting compound (R)-N,N-diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

13.1 (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine

[0083] To a stirred solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (Example 12) (10.2 g, 21.23 mmol) in DMF (100 mL) under nitrogen atmosphere at room temperature were sequentially added triethylamine (2.58 g, 25.47 mmol), TlOAc (6.15 g, 23.35 mmol), isobutylvinylether (14 mL, 106.14 mmol), DPPP (0.87 g, 2.12 mmol) and $Pd(OAc)_2$ (0.24 g, 1.06 mmol). The reaction temperature was raised to 100 °C and stirred for 3 hours, cooled to room temperature, filtered and treated with HCl (5%, 250 mL) and stirred for another 2 hours. The reaction mixture was repeatedly extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. Triethylamine and DMF were destilled off under reduced pressure to yield 9 g (98%); ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 12H), 2.52-2.70 (m, 7H), 3.40 (br, 2H), 4.34 (t, 1H), 5.10 (s, 1H), 6.90 (d, 1H), 7.17-7.40 (m, 10H), 7.82 (m, 1H) and 7.92 (s, 1H).

EXAMPLE 14

N,N-Diisopropyl-3(R)-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine fumarate

[0084] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine (2.7 g, 6.05 mmol) was hydrogenated over Pd/C (0.27 g, 10%) in ethanol at atmospheric pressure for 2 hours. The catalyst was filtered off and the solvent was evaporated. The resulting oil was chromatographed on silica (toluene-triethylamine 90:10). Fumarate salt of the amine was afforded by adding fumaric acid (0.13 g, 1.13 mmol) dissolved in warm ethanol to a solution of the free base in diethyl ether yielding white crystals (0.44 g, 83%); mp 240-244 °C; $[\alpha]_D$ +9.8° (c 1.02, methanol); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.26 (dd, 3H), 2.20-2.30 (m, 2H), 2.55-2.67 (m, 2H), 3.30 (m, 2H), 4.32 (t, 1H), 4.59 (q, 1H), 6.53 (s, 2H), 6.72 (dd, 1H), 6.93 (dd, 0.5H), 7.12-7.17 (m, 1H), 7.21-7.31 (m, 5H). Anal.

($C_{23}H_{33}NO_2 \cdot C_4H_4O_4 \cdot 0.3H_2O$) C, H, N.

[0085] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

14.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0086] N,N-Diisopropyl-3(R)-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine, prepared as described in Example 13.1, (3.5 g, 7.90 mmol) dissolved in dry THF was added to $LiAlH_4$ (0.2 g, 5.41 mmol). After 2 hours of stirring, additional $LiAlH_4$ (50 mg, 1.32 mmol) was added and the reaction mixture was stirred for 1.5 hours. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-E_3N 90:10) to give 2.74 g (78%) of an oil that crystallised slowly upon storage at room temperature.

EXAMPLE 15

(+)-N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine fumarate

[0087] N,N-Diisopropyl-3(R)-[2-benzyloxy 5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (0.55 g, 1.2 mmol) was treated in an analogous manner to that described in Example 14 above, which yielded white crystals, 0.32 g (55%); mp 196-200 °C; $[\alpha]_D$ +13.5° (c 1.0, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.40-2.48 (m, 1H), 2.52-2.60 (m, 1H), 3.03 (t, 2H), 3.55 (d, 2H), 3.66 (m, 2H), 4.42 (t, 1H), 4.57 (t, 1H), 6.7 (s, 2H), 6.79 (d, 1H), 7.05 (dd, 1H), 7.16-7.21 (m, 2H), 7.28 (m, 2H), 7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

[0088] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

15.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine

[0089] To an ice-chilled solution of AD-mix-α (5.7 g) in H_2O (20 mL) and t-BuOH (10 mL) was added N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (Example 12.1), (1.74 g, 4.1 mmol) dissolved in t-BuOH (10 mL). After 1 hour of stirring, the ice bath was removed and the reaction mixture was stirred for additional 21 hours. Na_2SO_3 (6 g) was then added and after 1 hours of stirring the reaction mixture was partioned between H_2O and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine, 90:10) to afford 0.55 g. ^1H NMR ($CDCl_3$) δ 0.9 (s, 6H), 0.95 (s, 6H), 2.15-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.96 (m, 2H), 3.60-3.70 (m, 2H), 4.41 (t, 1H), 4.75 (m, 1H), 5.0 (s, 2H), 6.85 (d, 1H), 7.10-7.35 (m, 12H).

EXAMPLE 16

(-)-N,N-Diisopropyl-3(R)-[5-(1(S*),2-dihydroxyethyl) 2-hydroxyphenyl]-3-phenylpropanamine fumarate

[0090] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (1.1 g, 2.4 mmol) was treated in an analogous manner to that described in Example 11 which yielded white crystals, 0.25 g (21%); mp 208-211 °C; $[\alpha]_D$ -8° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.39-2.47 (m, 1H), 2.51-2.59 (m, 1H), 3.03 (t, 2H), 3.51-3.53 (m, 2H), 3.67 (m, 2H), 4.42 (t, 1H), 4.54 (dd, 1H), 6.68 (s, 2H), 6.78 (d, 1H), 7.06 (dd, 1H), 7.16-7.20 (m, 2H), 7.26 (m, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

[0091] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was obtained by treating N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (obtained in Example 12.1) as described in Example 15.1 above, but with AD-mix-β replacing AD-mix-α. Yield 1.2 g (44%).

EXAMPLE 17

(R)-[N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine hydrochloride

[0092] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine (0.35 g, 0.72 mmol) was treated in an analogous manner to that described in Example 14. Yield 0.10 g (31%); mp 147-156 °C; $[\alpha]_D$ +8.2° (c 1.01, methanol); ^1H NMR (CD_3OD) δ 1.25-1.32 (m, 16H), 1.45-1.54 (m, 4H), 2.40-2.48 (m, 3H), 2.51-2.59 (m, 1H), 3.0-3.10 (m, 2H), 3.51 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.72 (d, 1H), 6.86 (dd, 1H), 6.91 (d, 1H), 7.19 (m, 1H), 7.30 (t, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{27}H_{41}NO_2 \cdot HCl \cdot 2H_2O$) C, N; H: calcd, 9.6; found, 8.3.

[0093] The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropan-

amine was prepared as follows:

17.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine

[0094] n-BuLi (2.5 M in hexane, 19 mL, 47.5 mmol) was added to a solution of to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3- phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8.9 g, 18.52 mmol) in dry diethyl ether (100 mL) kept at -40 °C under nitrogen atmosphere. After 1.5 hour of stirring, additional n-BuLi (10 mL, 25 mmol) was added and after 2 hours another n-BuLi (5 mL, 12.5 mmol) was added. The reaction was then stirred for 15 minutes and DMF (6 mL, 77.8 mmol) was added followed by additional DMF (5 mL, 64.8 mmol) after 20 minutes of stirring. The temperature was allowed to rise to room temperature and after 35 minutes of stirring, NH_4Cl (sat.) was added followed by water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (toluene-triethylamine 90:10) to afford 8 g (100%) of a yellowish oil; ^1H NMR ($CDCl_3$) δ 0.90 (m, 12H), 2.12-2.40 (m, 4H), 2.95 (m, 2H), 4.44 (t, 1H), 5.10 (s, 2H), 6.95 (d, 1H), 7.15-7.36 (m, 10H), 7.70 (dd, 1H), 7.91 (s, 1H), 9.88 (s, 1H).

17.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy 5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine

[0095] To a slurry of 4-carboxybutyl triphenylphosphonium bromide (4.1 g, 9.31 mmol) in THF (25 mL) at -10 °C under nitrogen atmosphere was added potassium tert-butoxide (2.1 g, 18.62 mmol). The mixture turned orange and after 10 minutes stirring, (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine (2 g, 4.65 mmol) in THF (10 mL) was added. After 4 hours of stirring, hydrochloric acid (1M) and diethyl ether were added and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine 90:10 followed by methanol) to afford 3 g containing traces of triphenylphosphine. The product was used in the next step without further purification.

17.3 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine

[0096] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine was reduced as described in Example 10. Yield 0.35 g (15%).

EXAMPLE 18

(R)-N,N-Diisopropyl-3-[5-(2-diisopropylaminoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0097] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine (0.6 g, 1.13 mmol) was refluxed with concentrated HCl (25 mL) overnight. The reaction mixture was then basified with 10 M sodium hydroxide and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.5 g oil that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. The resulting diethyl ether solution was treated with hydrogen chloride in diethyl ether. Yield 50 mg (9%); $[\alpha]_D$ +1.4° (c 0.94, methanol); ^1H NMR (CD_3OD) δ 1.27-1.34 (m, 12H), 1.36-1.42 (m, 12H), 2.50-2.58 (m, 1H), 2.60-2.67 (m, 1H), 2.95 (t, 2H), 3.05 (m, 2H), 3.15-3.27 (m, 2H), 3.70 (m, 2H), 3.75 (m, 2H), 4.40 (t, 1H), 6.80 (d, 1H), 7.02 (dd, 1H), 7.13 (d, 1H), 7.20 (m, 1H), 7.31 (m, 1H), 7.39-7.41 (m, 1H). Anal. ($C_{29}H_{46}N_2O \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

[0098] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine was prepared as follows:

18.1 N,N-Diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine

[0099] DMSO (1.1 mL, 15.5 mmol) dissolved in dichloromethane was added dropwise to oxalyl chloride (0.64 mL, 7.74 mmol) at -78 °C under nitrogen atmosphere. After 10 minutes of stirring, (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (Example 12.2) (2.3 g, 5.16 mmol) in dichloromethane was added and the reaction mixture was stirred for additional 1 h. Triethylamine (5.4 mL, 38.7 mmol) was then added and the temperature was allowed to rise to room temperature. The reaction mixture was taken up in water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the product was used in the next step without further purification.

18.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine

[0100] Diisopropylamine (4.2 mL, 30 mmol) was dissolved in methanol (12 mL). 5 M HCl in methanol (2 mL) was added followed by N,N-diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine (5 mmol) in methanol (10 mL) and sodium cyanoborohydride (0.22 g, 3.5 mmol). The reaction mixture was stirred at room temperature overnight. methanol was then evaporated, and diethyl ether and H_2O were added. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 3 g of a crude product that was chromatographed on silica (toluene-triethylamine 95:5). Yield 0.65 g (25%); ^1H NMR ($CDCl_3$) δ 0.88-0.91 (m, 18H), 1.20 (d, 9H), 2.10-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.87-3.10 (m, 4H), 4.34 (m, 1H), 4.98 (d, 2H), 6.75-6.97 (m, 2H), 7.10-7.30 (m, 11H).

EXAMPLE 19

(R)-N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine

[0101] (R)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (3.9 g, 11.5 mmol) and Al_2O_3 (115 g, 1.13 mol) refluxed in ethyl acetate (0.5 L) for 60 hours. Al_2O_3 was filtered off and ethyl acetate was evaporated. Chromatography on silica (toluene-triethylamine, 90:10) of the residue yielded 2.5 g (59%). The fumarate salt was obtained by adding fumaric acid (0.17 g, 1.48 mmol) dissolved in warm ethanol to the free base (0.55 g, 1.48 mmol) in diethyl ether; mp 174-177 °C; $[\alpha]_D$ +5.5° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.15 (t, 3H), 1.27-1.30 (m, 12H), 2.41-2.49 (m, 1H), 2.52-2.60 (m, 1H), 3.04 (dd, 2H), 3.49 (q, 2H), 3.67 (m, 2H), 4.35 (s, 2H), 4.43 (t, 1H), 6.69 (s, 2H), 6.80 (d, 1H), 7.04 (dd, 1H), 7.12 (d, 1H), 7.18-7.37 (m, 4H). Anal. ($C_{24}H_{35}NO_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 20

N-Isopropyl-3-(5-carboxy-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0102] N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine (1.3 g, 2.6 mmol) was dissolved in HOAc. Palladium (10%) on charcoal (0.13 g) was added and the mixture was hydrogenated at atmospheric pressure for 48 hours. The catalyst was then filtered off and the solvent was evaporated. The resulting oil was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). This purification was done in 16 portions with about 100 mg material each time. The pure fractions were pooled and freeze-dried to give 0.57 g of trifluoroacetic acid salt. The crystals were dissolved in 1 M HCl and freeze-dried to give 0.4 g (43%) of the hydrochloride salt as white crystals; mp 155-160 °C; ^1H NMR (DMSO-d_6) δ 1.17 (d, 3H), 1.19 (d, 3H), 2.30-2.38 (m, 1H), 2.38-2.46 (m, 1H), 2.72 (br, 1H), 2.80 (br, 1H), 3.25 (m, 1H), 4.40 (t, 1H), 6.94 (d, 1H), 7.18-7.22 (m, 1H), 7.29-7.33 (m, 4H), 7.66 (dd, 1H), 7.76 (d, 1H); Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

[0103] The starting compound N-benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine was prepared as follows:

20.1 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal

[0104] 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanol (16.5 g, 41.5 mmol) (prepared as described in WO 94/11337, Example 1c) was reacted as described in Example 18.1. The combined organic layers were washed with 2 M HCl, 10% $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated to give 16 g (98%) of yellowish crystals of the product that was used in the next step without further purification; mp 99-100 °C; ^1H NMR ($CDCl_3$) δ 3.10 (dd, 2H), 5.0 (s, 2H), 4.98-5.10 (m, 1H), 6.76 (d, 1H), 7.16-7.38 (m, 12H), 9.65 (s, 1H).

20.2 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0105] To a solution of N-benzylisopropylamine (34 mL, 0.20 mol) in methanol (80 mL) was added 5 M HCl in methanol (16.2 mL, 80.9 mmol) followed by 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (16.0 g, 40.5 mmol) in methanol (20 mL) and sodium cyanoborohydride (1.78 g, 28.3 mmol). The resulting solution was stirred for 17 hours. The solvent was evaporated and diethyl ether was added to the resulting syrup. The solution was washed 3 times with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (hexane-ethyl acetate, 75:25) giving 15.9 g of a syrup. The hydrochloride salt of the compound was prepared by dissolving the product in diethyl ether and adding HCl dissolved in diethyl ether. The resulting oil was washed with diethyl ether, dissolved in 10 M sodium hydroxide and extracted with diethyl ether 3 times. Purification by chromatography on silica (using a gradient of dichloromethane up

to 1% triethylamine in dichloromethane) yielded 7 g (33%) of the product as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H), 0.90 (d, 3H), 2.02-2.12 (m, 2H), 2.38 (t, 2H), 2.90 (m, 1H), 3.50 (d, 2H), 4.50 (t, 1H), 4.95 (s, 2H), 6.70 (s, 1H), 7.10-7.35 (m, 17H).

20.3 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine

[0106] A mixture of magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal) was warmed gently. A solution of N-benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (6.0 g, 11 mmol) and 1,2-dibromoethane (0.2 mL, 2.3 mmol) in dry THF (25 mL) was added dropwise under nitrogen atmosphere to the refluxing mixture. After 2 hours of refluxing, 1,2-dibromoethane (0.59 mL, 6.8 mmol) was added. The mixture was left overnight under nitrogen atmosphere. The mixture was then added together with 1,2-dibromoethane (0.93 mL, 10.8 mmol) to warmed magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal). After 30 minutes of refluxing, the mixture was cooled to room temperature and CO_2 (g) was bubbled through. After 3 hours, ammonium chloride (aq, 15%, 50 mL) was added followed by diethyl ether (100 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated to give 5.8 g of an oil. The crude product was chromatographed on silica (using a gradient of acetone up to 5% ethanol in acetone) to give the pure product (1.3 g, 23%) as an oil. N-benzyl-N-isopropyl-3-(2-benzyloxyphenyl)-3-phenylpropanamine (3.1 g) was obtained as a biproduct from the reaction. ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 3H), 1.10 (d, 3H), 2.30-2.40 (m, 2H), 2.46-2.65 (m, 2H), 3.40 (br, 1H), 3.85 (br, 2H), 4.30 (br, 1H), 4.98 (br, 2H), 6.80 (d, 1H), 7.10-7.40 (m, 15H), 7.95 (d, 1H), 7.95 (d, 1H), 8.20 (s, 1H).

EXAMPLE 21

N-Benzyl-N-isopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0107] N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine, prepared as described in Example 20.3, (3.1 g, 6.90 mmol) was refluxed in concentrated HCl (30 mL) for 20 h. The reaction mixture was allowed to cool to room temperature and the liquid was poured off. The remaining oil was washed with water and diethyl ether and then dissolved in 2-propanol. The solution was evaporated and treated with 10 M sodium hydroxide to give the free base. Chromatography on silica (hexane:ethyl acetate 75:25) afforded 0.5 g of the compound that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. To the resulting diethyl ether solution was added dropwise saturated diethyl ether-HCl (g). The resulting crystals of the hydrochloric salt were collected by filtration; mp 115-122 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 6H), 2.27-2.38 (m, 1H), 2.48-2.55 (m, 1H), 2.72-2.97 (m, 2H), 3.55 (m, 1H), 4.23 (m, 2H), 4.35 (m, 1H), 6.68-6.74 (m, 1H), 6.82 (dt, 1H), 6.96-7.24 (m, 7H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H), 9.55 (d, 1H), 10.62 (br, 1H). Anal. ($C_{25}H_{29}NO\cdot HCl$) C, H, N.

EXAMPLE 22

(R)-N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine dihydrochloride

[0108] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine (3.20 g, 7.07 mmol) was dissolved in 100 % acetic acid and 10% Pd/C (0.52 g) was added. The mixture was hydrogenated (60 psi) overnight at room temperature. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in water, basified with sodium hydroxide (11 M), extracted with ethyl acetate, the organic phase was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (toluene-ethyl acetate-triethylamine-methanol, 20:5:1.5:1). The amine was redissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate was filtered off wich gave 0.30 g (10 %); ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 1.88 (m, 2H), 2.51(m, 2H), 2.59 (t, 2H), 2.88 (t, 2H), 3.04 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 4.55 (bs, 1H), 6.76 (d, 1H), 6.93 (d, 1H), 7.03 (s, 1H), 7.19 (t, 1H), 7.30 (t, 2H), 7.37 (d, 2H); mp. 226-228 °C; $[\alpha]_D$ +11.5° (c=1.0, methanol). Anal. ($C_{24}H_{36}N_2O$*2HCl) C, H, N.

[0109] The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine was prepared as follows:

22.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyano-ethenyl)phenyl]-3-phenylpropylamine

[0110] To a solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (13.87 g, 28.87 mmol) (prepared as described in WO 94/11337, Example 1) in DMF (140 mL) was added triethylamin (5.00 mL, 36.10 mmol), $Pd(OAc)_2$ (0.32 g, 1.44 mmol), tri(o-tolyl)phosphine (1.76 g, 5.77 mmol) and acrylonitrile (2.39 mL, 36.10 mmol). The reaction mixture was stirred overnight at 115 °C in a sealed flask equipped with a reflux condenser under nitrogen

atmosphere. The resulting mixture was concentrated, and the residue was dissolved in diethyl ether, washed with aqueous 2 M sodium hydroxide and water. The organic phase was dried ($MgSO_4$) whereafter petroleum ether was added to the organic phase and a precipitate was formed. Recrystallisation from ethanol yielded 5.50 g (42%). ^1H NMR ($CDCl_3$) δ 0.90 (s, 6H), 0.95 (s, 6H), 2.15 (q, 2H), 2.35 (q, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.05 (s, 2H), 5.70 (d, 1H), 6.85 (d, 1H), 7.10-7.50 (m, 13H).

EXAMPLE 23

(R)-N,N-Diisopropyl-3-[5-3-(acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0111] To a solution of (R)-N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, (Example 22), (0.45 g, 1.23 mmol) in methanol (45 mL) was added acetic anhydride (0.23 mL, 2.47 mmol). The mixture was stirred for 3 h at room temperature and then evaporated to dryness. The residue was dissolved in H_2O, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried with $MgSO_4$, filtered and evaporated. The amine was dissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate formed was filtered off to give 0.55 g (100 %). ^1H NMR (CD_3OD) δ 1.27 (m, 12H), 1.75 (m, 2H), 2.08 (s, 3H), 2.52 (m, 4H), 3.04 (t, 2H), 3.20 (t, 2H), 3.68 (m, 2H), 4.40 (t, 2H), 6.72 (d, 1H), 6.90 (d, 1H), 6.99 (s, 1H), 7.19 (t, 1H), 7.30 (m, 4H); mp. 171-175 °C; $[a]_D$ +3.6° (c=0.5, methanol). ($C_{26}H_{38}N_2O_2$*HCl) C, H, N.

EXAMPLE 24

(R)-N,N-Diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0112] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropylamine (Example 22.1), (4.00 g, 8.84 mmol) was treated as described in Example 22, but the hydrogenation was performed at atmospheric pressure. Yield 1.35 g (38 %); ^1H NMR (CD_3OD) δ 1.14 (s, 6H), 1.16 (s, 6H), 2.50 (m, 2H), 2.79 (t, 2H), 3.05 (t, 2H), 3.68 (m, 2H), 4.39 (t, 2H), 6,75 (d, 1H), 6.98 (d, 1H), 7.09 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 156-159 °C; $[\alpha]_D$+4.0° (c=0.5, methanol); Anal. ($C_{24}H_{32}N_2O$*1.0HCl*0.25H_2O) C, H; N: calcd, 6.9; found, 6.4.

EXAMPLE 25

(R)-N,N-Diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride.

[0113] A solution of (R)-N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine (Example 24), (2.00 g, 5.48 mmol), in conc. HCl was stirred at 50 °C for 2 h and then evaporated. The residue was dissolved in water, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was chromatographed on toluene-ethyl acetate-triethylamine-methanol, 7:2:1:1. The product was obtained from dietyl ether-hydrogen choride. Yield 0.9 g (39%); ^1H NMR (CD_3OD) δ 1.31 (m, 12H), 2.44 (t, 2H), 2.53 (m, 2H), 2.78 (t, 2H), 3.04 (t, 2H), 3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.82 (d, 1H), 7.02 (s, 1H), 7.18 (t, 1H), 7.32 (m, 4H); mp. 200-202 °C; $[\alpha]_D$ +7.6° (c=0.5, methanol). Anal. ($C_{24}H_{34}N_2O_2$*1.0HCl *0.5H_2O) C, H, N.

EXAMPLE 26

(R)-N,N-Diisopropyl-3-[5-(2-carboxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0114] To a solution of (R)-N,N-diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (obtained in Example 25), (0.50 g, 1.31 mmol) in ethanol (15 mL) and H_2O (10 mL) was added KOH (3.75 g, 66.8 mmol). The mixture was stirred overnight at 100 °C. The solvent was evaporated and the residue redissolved in H_2O and washed with diethyl ether. The aqueous layer was acidified with conc. HCl and the precipitate was collected by filtration and washed with 2 M HCl. The product was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using a gradient of 20-60% acetonitrile with 0.1% TFA. Fractions were pooled and hydrochloric acid (2 mL, conc.) was added and the solvent was evaporated. The residue was crystallised from methanol-diethyl ether to give 0.37 g (0.96 mmol, 74%); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 4H), 2.76 (t, 2H), 3.04 (t, 2H), 3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.92 (d, 1H), 7.00 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 205-207 °C; $[\alpha]_D$ +3.7° (c=1.0, methanol). Anal. ($C_{24}H_{33}NO_3$*1.0HCl) C, H, N.

EXAMPLE 27

(R)-(N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine dihydrochloride

[0115] (R)-N,N-Diisopropyl-3- (5-azido-2-benzyloxyphenyl) -3-phenylpropanamine (0.90 g, 2.03 mmol) was dissolved in acetic acid and 10% Pd/C (210 mg, cat.) was added. The mixture was stirred and exposed to H_2 (1 atm.) at room temperature overnight. The Pd/C catalyst was filtered off, and the filtrate evaporated. The residue was dissolved in water and basified with aqueous 11 M sodium hydroxide, extracted with diethyl ether, dried ($MgSO_4$) filtrated and evaporated. The crude residue was chromatographed on silica (n-hexane-ethanol-triethylamine, 7:3:1). The hydrochloride was obtained from dietyl ether hydrogen chloride. The resulting oil was freeze-dried from water. Yield 0.30 g (37 %); ^{1}H NMR (DMSO) δ 1.13 - 1.33 (m, 12H), 2.47 (m, 2H), 2.82 (br, 1H), 2.98 (br, 1H), 3.57 (br, 2H), 4.38 (t, 1H), 6.96 (d, 1H), 7.08 (d, 1H), 7.19 (s, 1H), 7.22 (m, 1H), 7.32 (m, 4H), 10.05 (br, 2H), 10.13 (s, 1H); mp. 180-183 °C; $[\alpha]_D$ +21.0° (c=0.1, methanol). Anal. ($C_{21}H_{30}N_2O$*2.0HCl*0.5H_2O) C, H, N.

[0116] The starting compound (R)-N,N-diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

27.1 (R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine

[0117] To a mixture of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (10.00 g, 20.81 mmol) (prepared as described in WO 94/11337, Example 1) and Mg (1.57 g, 64.52 mmol) in THF (50 mL) was added 1,2-dibromoethane (3.59 mL, 41.63 mmol) and the solution was self-refluxing for a while. The mixture was refluxed for 1 h whereafter the solution was cooled and tosyl azide (4.10 g, 20.81 mmol) in diethyl ether (100 mL) was added with constant stirring while keeping the temperature at 0 °C wherafter the temperature was allowed to rise to room temperature for 4 h. A solution of tetra-sodium pyrophosphate decahydrate (4.46 g, 10.00 mmol) in 50 mL water was added. A precipitate was filtered off and the filtrate was evaporated. The residue was extracted with diethyl ether, the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (n-hexane-ethanol, 8:2). The product was crystallised from ethanol to give 1.15 g (13 %); IR (KBr) 2116 (N_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 12H), 2.10 (m, 2H), 2.33 (m, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.00 (s, 2H), 6.81 (d, 2H), 6.97 (s, 1H), 7.10 - 7.40 (m, 10H).

EXAMPLE 28

(R)-N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0118] To a solution of (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine (0.25 g, 0.76 mmol) in 0.78 M HCl (5.35 mL, 4.20 mmol) was added $NaNO_2$ (0.05 g, 0.76 mmol) dissolved in H_2O (0.4 mL) at -10 °C and the mixture was stirred for 20 minutes. To the mixture was added NaN_3, (57 mg, 0.88 mmol) dissolved in H_2O (0.4 mL), and the mixture was stirred at -10 °C for 30 minutes. The mixture was basified (pH 7-8) with aqueous 11 M sodium hydroxide and extracted with diethyl ether. The diethyl ether phase was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:2:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The precipitate was filtered to give (0.07 g, 0.18 mmol, 24%) of light-brown crystals. IR (KBr) 2111 (N_3) cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 2.50 (m, 2H), 3.04 (m, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.68 (s, 1H), 6.81 (m, 2H), 7.23 (m, 1H), 7.35 (m, 4H); mp. 131-134 °C; $[\alpha]_D$-5.0° (c=0.1, methanol).

[0119] The starting compound (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine was prepared as follows:

28.1 (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine

[0120] A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (7.30 g, 15.2 mmol) treated as described in Example 1.3 above. Yield 4.47 g (94 %).

28.2 (R)-N,N-Diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine

[0121] $NaNO_2$ (0.27 g, 4.30 mmol) was added to a mixture of hydrochloric acid (0.64 mL, 7.70 mmol, conc.) and p-methylaniline (0.41 g, 3.80 mmol) in ice-water (20 mL). The mixture was stirred at 0 °C for 10 min. and then added to an ice-cold solution of (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine (1.00 g, 3.21 mmol) in THF (3mL), H_2O (12 mL) and sodium hydroxide (0.69 g, 17.32 mmol). After stirring the mixture for 20 minutes, it was extracted with toluene, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on (toluene-ethyl acetate-triethylamine 8:1:1) to give 0.83 g, 1.93 mmol, (60%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 6H),

1.19 (d, 6H), 2.22 (m, 1H), 2.43 (m, 5H), 2.79 (m, 1H), 3.32 (m, 2H), 4.57 (d, 1H), 6.98 (d, 1H), 7.24 (m, 3H), 7.36 (m, 4H), 7.66 (m, 4H).

28.3 (R)-N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine

[0122] A solution of $Na_2S_2O_4$ (1.23 g, 12.8 mmol) in water (10 mL) was added to a solution of (R)-N,N-diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine (0.55 g, 1.28 mmol) in ethanol (50 mL) at 75 °C during 15 min. More dry $Na_2S_2O_4$ (1.23 g, 12.8 mmol) was added in 10 portions. Water was added to the solution which was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (n-hexane-ethanol-triethylamine 7:3:1) to give an oil. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. The solvent was evaporated, redissolved in water and vacuum-dried wich yielded 0.25 g (60%).

EXAMPLE 29

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine hydrochloride

[0123] A solution of (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (2.0 g, 4.86 mmol) in THF (50 mL) was added dropwise to LAH (0.28 g, 7.29 mmol). After stirring for 2 h, the reaction was quenched and the solvent evaporated. The residue was recrystallized from ethanol-water. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. White crystals were filtered off to give 0.82 g (46%); mp. 204-207 °C; $[\alpha]_D$ +12.8° (c=1.0, methanol); ^1H NMR (DMSO) δ 1.18 (t, 6H), 1.24 (t, 6H), 1.63 (m, 2H), 2.47 (m, 4H), 2.87 (br, 2H), 3.38 (q, 2H), 3.57 (br, 2H), 4.32 (t, 1H), 4.42 (t, 1H), 6.74 (d, 1H), 6.83 (d, 1H), 7.03 (s, 1H), 7.17 (t, 1H), 7.30 (m, 4H) Anal. ($C_{24}H_{35}NO_2$*1.0HCl) C, H, N.

[0124] The starting compound (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine was prepared as follows:

29.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine

[0125] A solution of triethyl phosphonoacetate (6.93 mL, 34.92 mmol) in THF (50 mL) was added dropwise to NaH (0.84 g, 29.10 mmol, 80%). The mixture was cooled to 0 °C and (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine, prepared as described in Example 17.1, (5.00 g, 11.64 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 3 h at 0 °C. The solvent was evaporated and the residue was redissolved in toluene and washed twice with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 5.0 g (86%).

29.2 (R)-N,N-Diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine

[0126] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine (3.0 g, 5.98 mmol) was treated as described in Example 1.3. Yield 2.0 g (81%); ^1H NMR ($CDCl_3$) δ 1.08 (d, 6H), 1.12 (d, 6H), 1.18 (t, 3H), 2.05 (m, 2H), 2.37 (m, 4H), 2.72 (t, 2H), 3.22 (m, 2H), 4.03 (q, 2H), 4.48 (m, 1H), 6.55 (s, 1H), 6.86 (m, 2H), 7.28 (m, 5H).

EXAMPLE 30

N,N-Diisopropyl-3-(5-ethylaminomethyl-2-hydroxyphenyl)-3-phenylpropanamine

[0127] (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (prepared in Example 7.1) (1.23 g, 3.62 mmol) was dissolved in methanol (20 mL). Ethylamine [3.62 mL, 21.7 mmol (6M hydrochloric acid in methanol)] and sodium cyanoborohydride (0.14 g, 2.17 mmol) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:3:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The resulting oil was stirred in diethyl ether over night to give crystals. Yield 0.70 g (44%); mp. 140-142 °C; $[\alpha]_D$ -5.0° (c=0.5, methanol); ^1H NMR (CD_3OD) δ 1.30 (m, 15H), 2.59 (m, 2H), 3.05 (m, 4H), 3.70 (m, 2H), 4.07 (s, 2H), 4.42 (t, 1H), 6.85 (d, 1H), 7.20 (m, 2H), 7.30 (t, 2H), 7.41 (d, 2H), 7.50 (s, 1H) Anal. ($C_{24}H_{36}N_2O$*2.0HCl*0.5H_2O) C,H,N.

EXAMPLE 31

N-Cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0128] A solution of N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (1.60 g, 3.44 mmol) was hydrogenated over Pd/C (160 mg, 10%) in acetic acid at room temperature overnight. The solution was basified with sodium hydroxide (11 M) and the mixture was filtered. The filtrate was extracted with ethyl acetate, dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluen-triethylamine 9:1). The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to give an oil. The oil was crystallised in 2-propanol to give 0.90 g (79%); mp. 153-155 °C; ^{1}H NMR (CD_3OD) δ 1.78 (m, 2H), 2.22 (m, 4H), 2.48 (m, 2H), 2.72 (s, 3H), 2.95 (br, 2H), 3.68 (m, 1H), 4.44 (t, 1H), 6.78 (t, 1H), 6.79 (d, 1H), 7.03 (t, 1H), 7.12 (d, 1H), 7.18 (t, 1H), 7.28 (t, 2H), 7.34 (d, 2H); Anal. ($C_{20}H_{25}NO$*1.0 HCl*0.3 2-propanol) C, H, N.

[0129] The starting compound N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

31.1 N-Cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0130] 5 M HCl-methanol (3.50 mL, 17.71 mmol) was added to a solution of cyclobutylamine (4.50 mL, 53.15 mmol) in methanol (14 mL). The mixture was added to 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (Example 20.1), (3.50 g, 8.86 mmol), followed by sodium cyanoborohydride (0.389 g, 6.20 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 92:4:4).Yield 2.61 g (65%); ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 5H), 2.14 (m, 4H), 2.47 (t, 2H), 3.16 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.47 (m, 12H).

31.2 N-Cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0131] 5 M HCl-methanol (0.46 mL, 2.32 mmol), formaldehyde (0.870 g, 28.97 mmol) and sodium cyanoborohydride (0.255 g, 4.056 mmol) were added to a solution of N-cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.61 g, 5.79 mmol) in methanol (8 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (hexane-triethylamine, 9:1). Yield 1.59 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.73 (m, 2H), 1.91 (m, 2H), 2.06 (s, 3H), 2.16 (m, 4H), 2.68 (m, 1H), 4.38 (t, 1H), 5.00 (s, 2H), 6.72 (d, 1H), 7.12-7.58 (m, 12H).

EXAMPLE 32

N-Cyclopentyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0132] N-Cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.46 g, 5.14 mmol) was treated as described in Example 31. The crude was not chromatographed but crystallised from aqueous ethanol. Yield 1.24 g (70%) ^{1}H NMR (DMSO) δ 1.48 (br, 1H), 1.66 (br, 2H), 1.85 (br, 1H), 2.46 (br, 2H), 2.68 (s, 3H), 2.87 (br, 2H), 3.53 (m, 1H), 4.35 (t, 1H), 6.77 (t, 1H), 6.83 (d, 1H), 7.01 (t, 1H), 7.16 (t, 1H), 7.27 (t, 3H), 7.33 (d, 2H), 9.57 (br, 1H), 10.85 (br, 1H); mp 169-172 °C; Anal. ($C_{21}H_{27}NO$*HCl) C, H, N.

[0133] The starting compound N-cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

32.1 N-Cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0134] 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal, prepared as described in Example 20.1, (7.00 g, 17.71 mmol) was treated with cyclopentylamine as described in Example 31.1. Yield 4.9 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 2H), 1.40-1.80 (m, 6H), 2.18 (m, 2H), 2.55 (t, 2H), 2.98 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.45 (m, 12H).

32.2 N-Cyclopenthyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0135] A solution of N-cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (3.50 g, 7.53 mmol) was treated as described in Example 31.2. Yield 2.46 g (68%); ^{1}H NMR ($CDCl_3$) δ 1.10-1.80 (m, 8H), 2.19 (m, 5H), 2.36 (m, 2H), 2.58 (m, 1H), 4.37 (t, 1H), 4.98 (s, 2H), 6.72 (d, 1H), 7.10-7.50 (m, 12H).

EXAMPLE 33

N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropanaminehydrochloride

[0136] LAH (0.94 g, 24.8 mmol) was added to a solution of N,N-diisopropyl-3-(2-aminophenyl) -3-phenylpropenylamide (1.6 g, 4.98 mmol) in THF (90 mL). The mixture was stirred for 72 h at room temperature. The reaction was quenched and the solvent evaporated. The crude residue was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using 20 % acetonitrile with 0.1% TFA. Hydrochloric acid was added to the pure fractions and the solvent was evaporated. The residue was redissolved in water and freeze-dried giving 88 mg (5%) ; mp 138 - 142 °C; ^{1}H NMR (DMSO) δ 1.25 (m, 12H), 2.47 (m, 1H), 2.65 (m, 1H), 2.87 (m, 1H), 3.13, (m, 1H), 3.59 (br, 2H), 4.58 (t, 1H), 7.20 - 7.37 (m, 5H), 7.42 (m, 2H), 7.54 (d, 2H), 9.94 (br, 2H). Anal. ($C_{21}H_{30}N_2$*HCl*H_2O) C, N, H: calcd.8.5; found 7.9.

[0137] The starting compound N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide was prepared as follows:

33.1 2-(3,5-Dimethyl-4-hydroxyphenylazo)benzophenone

[0138] A slurry of ice (500 mL), hydrochloric acid (16.8 mL, 202 mmol, conc.), 2-aminobenzophenone (20.00 g, 101 mmol) and $NaNO_2$ (9.0 g, 131 mmol) were added to a stirred solution of 2,6-dimethylphenol (18.40 g, 151 mmol) and sodium hydroxide (16.20 g, 404 mmol) in ice-cold water (100 mL). After 20 minutes the mixture was extracted with diethyl ether. The organic phase was washed with hydrochloric acid (6 M), $NaHCO_{3(aq)}$, dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene) and pure fractions were pooled and evaporated to give a red oil. The oil was crystallised in hexane/toluene to give 7.73 g (23%).

33.2 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone

[0139] A mixture of 2-(3,5-dimethyl-4-hydroxyphenylazo)-benzophenone (7.73 g, 23.41 mmol) and tosyl chloride (9.4 g, 49 mmol) in pyridine (20 mL) was stirred at 90 °C for 9 h. Water was added and the mixture was extracted with diethyl ether. The organic phase was washed with sodium hydroxide (2 M) and hydrochloric acid (2 M), dried ($MgSO_4$) and the solvent evaporated. The product was crystallised in ethanol to give 7.62 g (67%); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 6H), 2.49 (s, 3H), 7.05 (s, 2H), 7.37 (m, 4H), 7.48 (m, 1H), 7.62 (m, 3H), 7.82 (m, 5H).

33.3 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenylazo)phenyl]-3-phenylpropenamide

[0140] 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone (7.22 g, 14.9 mmol) was treated as described in Example 4.2 but with 3 eq of N,N-diisopropylacetamide diethylphosphonate and sodium hydride. Yield 4.5 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H), 0.82 (br, 3H), 1.28 (d, 3H), 1.42 (d, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.45 (s, 3H), 3.25 (m, 1H), 4.28 (m, 1H), 6.05 and 6.63 (s, 1H), 7.00 - 7.90 (m, 15H).

33.4 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenylazo)phenyl]-3-phenylpropenamide

[0141] A solution of potassium hydroxide (10.3 mL, 6 M) and N,N-diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenylazo)phenyl]-3-phenylpropenamide (3.5 g, 5.74 mmol) in ethanol (110 mL) was refluxed for 1 h. The mixture was acidified with hydrochloric acid (conc.) and the solvent evaporated. The residue was partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene-ethyl acetate 9:2). Yield 1.3 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.71 (d, 3H), 0.80 (br, 3H), 1.27 (d, 3H), 1.40 (d, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.25 (m, 1H), 4.35 (m, 1H), 5.52 (brd, 1H), 6.05 and 6.60 (s, 1H), 7.00 - 7.80 (m, 11H).

33.5 N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropenamide

[0142] N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenylazo)phenyl]-3-phenylpropenamide (2.58 g, 5.68 mmol) was treated as described in Example 28.3. The crude residue gave crystals from aqueous ethanol. Yield 1.23g (67%).

EXAMPLE 34

N,N-Diisopropyl-3-(benzoxazol-2-yl)-3-phenylpropanamine,hydrochloride

[0143] A mixture of N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (2.51 g, 8.6 mmol), 75% aqueous ethanol (15 mL) and 2 M NaOH (8.5 mL, 17 mmol) was refluxed over night. After evaporation of the solvent, the residue

was made acidic with 2 M HCl and the solvent was evaporated. A mixture of the residual semicrystalline oil was heated with o-aminophenol (1.8 g, 16.5 mmol) and polyphosphoric acid (12 g) at 200°C for 2 hours under N_2. The somewhat cooled hard solid was dissolved in water and washed once with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether/triethylamine 97:3). The pure amine was precipitated as hydrochloride from diethyl ether affording white crystals, 1.27 g (39%): mp 197-198°C; ^1H NMR ($CDCl_3$) δ 1.49 (m, 12H), 2.80-3.20 (m, 4H), 3.48 (br, 2H), 4.45 (t, 1H), 7.25-7.48 (m, 8H), 7.70 (m, 1H), 11.48 (br, 1H).

[0144] The starting compound N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine was prepared as follows:

34.1 N,N-Diisopropyl-3-cyano-3-phenylpropanamine

[0145] Sodium hydride, 80% in mineral oil (2.82 g, 94 mmol), was washed with petroleum ether and dried under a N_2-stream. Dry DMF (100 mL) was added. Benzyl cyanide (12.1 g, 103 mmol) was added to the stirred suspension over a period of 20 min. The temperature rose to approx. 45°C. The mixture was stirred for another 15 min. 2-Chloroethyldiisopropylamine (15.4 g, 94 mmol) was added. All the amine was consumed within 30 min. Most of the DMF was evaporated under reduced pressure and the residue was dissolved in water/diethyl ether. The aqueous phase was extracted once with diethyl ether and the combined organic phases were extracted twice with 2 M HCl. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent was evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 40:1), affording the title compound, 16.8 g (67%), as a colourless liquid. ^1H NMR ($CDCl_3$) δ 1.01 (m, 12H), 1.97 (m, 2H), 2.62 (m, 2H), 3.00 (m, 2H), 4.02 (dd, 1H), 7.17-7.40 (m, 5H).

34.2 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamine

[0146] N,N-Diisopropyl-3-cyano-3-phenylpropanamine (11.6 g, 47.5 mmol) was mixed with H_2SO_4 (90%, 100 mL) and the mixture was stirred at 100°C for 30 min. The reaction mixture was poured on ice, made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated, affording the title compound as a colourless oil, 12.4 g (100%); ^1H NMR ($CDCl_3$) δ 1.26 (m, 12H), 2.14 (m, 1H), 2.60 (m, 1H), 2.73 (t, 2H), 3.31 (m, 2H), 3.86 (t, 1H), 6.06 (br, 2H), 7.51- 7.61 (m, 5H).

34.3 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine

[0147] N,N-Diisopropyl-3-carbamyl-3-phenylpropanamine (26.5 g 0.100 mol) was added into aqueous ethanol (90%, 300 mL) containing conc. HNO_3 (13.3 g, 0.21 mol) and refluxed for five days. Most of the solvent was evaporated under reduced pressure and the residue was mixed with water/diethyl ether. The organic phase was washed once with water. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 97/3), to afford the title compound as a colourless liquid, 20.1 g (68.7%): ^1H NMR ($CDCl_3$) δ 0.96 (m, 12H), 1.21 (t, 3H), 1.81 (m, 1H), 2.22 (m, 1H), 2.40 (t, 2H), 3.66 (dd, 1H), 4.12 (m, 2H), 7.20-7.32 (m, 5H).

EXAMPLE 35

N,N-Diisopropyl-3-(oxazol-5-yl)-3-phenylpropanaminehydrochloride

[0148] Freshly distilled methylisonitrile (1.66 g, 40.4 mmol) was dissolved in dry THF (75 mL) under N_2-atmosphere and the mixture was cooled to -78°C. 1.4 M n-BuLi (29 mL, 40.5 mmol) was slowly added to the solution, followed by N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (4.71 g, 16.2 mmol) in THF (10 mL). The reaction temperature was allowed to rise to -20°C, at which the reaction was quenched with HOAc (10 mL). The solvent was evaporated and the residue was mixed with diethyl ether/water. The organic phase was washed once with water and the combined aqueous phases were made alkaline with 11 M NaOH and extracted twice with diethyl ether. The organic phases were put together, dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 490:10:1). The pure amine was precipitated with HCl-saturated diethyl ether, affording the title compound as a glassy oil, 1.4 g (48%). ^1H NMR (CD_3OD) δ 1.21-1.40 (m, 12H), 2.57 (m, 1H), 2.68 (m, 1H), 2.91 (m, 1H), 3.23 (m, 1H), 3.72 (m, 2H), 4.41 (dd, 1H), 7.39 (m, 5H), 7.52 (s, 1H), 9.13 (s, 1H).

EXAMPLE 36

N,N-Diisopropyl-3-(imidazol-4(5)-yl)-3-phenylpropanamine dihydrochloride

[0149] N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was mixed with formamide (5 mL). The mixture was heated at 175°C for 6 hours. The solvent was evaporated under vacuum (1 mm Hg) and the residue was partitioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The light brown oil was dissolved in diethyl ether and added to a suspension of lithium aluminium hydride (LAH) (0.70 g, 5.4 mmol) in diethyl ether. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched, and the solvent was evaporated. The crude amine was dissolved in EtOAc and precipitated as a hydrochloride salt with HCl-saturated diethyl ether to afford the title compound as hygroscopic crystals, 0.32 g (35%) : ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 12H), 2.80 (m, 2H), 3.00 (m, 1H), 3.16 (m, 1H), 3.64 (br, 2H), 4.41 (m, 1H), 6.89 (s, 1H), 7.27-7.41 (m, 5H), 8.78 (s, 1H), 10.32 (br, 2H).

[0150] The starting compound N,N-diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was prepared as follows:

36.1 3-Cyano-3-phenylpropanoic acid

[0151] Ethyl cinnamate (85.3 g, 0.484 mol), potassium cyanide (64.2 g, 0.986 mol) and ammonium chloride (38.9 g, 0.726 mol) were mixed with aqueous DMF (90%, 360 mL). The mixture was stirred at 105°C for 7 hours. The somewhat cooled mixture was filtered and most of the DMF was evaporated. The residue was taken up in diethyl ether and 1 M HCl. The aqueous phase was extracted twice with diethyl ether. The combined diethyl ether phases were evaporated and the black oil was suspended in EtOH (200 mL) and 2 M NaOH (250 mL) and stirred at ambient temperature for 2 hours. The mixture was diluted with brine (200 mL) and water (400 mL) and washed twice with diethyl ether. After acidification (12 M HCl) the aqueous phase was extracted three times with diethyl ether. The pooled organic phases were dried (Na_2SO_4) and the solvent evaporated affording the title compound as a black oil, 74 g (87%): ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.17 (d, 3H), 1.22 (d, 6H), 2.68 (dd, 1H), 3.16 (dd, 1H), 3.4 (br, 1H), 3.76 (m, 1H) 4.19 (dd, 1H), 7.31 (m, 5H), 8.9 (br, 1H).

36.2 N,N-Diisopropyl-3-cyano-3-phenylpropanamide

[0152] 3-Cyano-3-phenylpropanoic acid (67.7 g, 0.389 mol) was dissolved in 2-PrOH. To the filtered acid solution was carefully added KOH (18.4 g, 0.33 mol) dissolved in 2-PrOH (200 mL), diethyl ether (100 mL) was added and the precipitate was filtered off. The dried acid salt (51.9 g, 0.24 mol) was suspended in benzene (400 mL) and oxalyl chloride was carefully added. The reaction mixture was stirred at 80°C for 2 hours. The solvent was evaporated and the residue was co-evaporated twice with benzene. The brown oil was dissolved in benzene (200 mL) and cooled in an icebath. A solution of diisopropylamine (82 g, 0.81 mol) in benzene (200 mL) was added to the stirred reaction mixture during 45 min. The mixture was left to slowly warm up to room temperature overnight. The solvent was evaporated and the residue was taken up in diethyl ether and 1 M HCl. The organic phase was washed once with water, once with 1 M NaOH, again with water, dried (Na_2SO_4) and the solvent evaporated to afford the title compound as a dark brown oil, 41.7 g (41%): ^{1}H NNR ($CDCl_3$) δ 1.07 (d, 3H), 1.17 (d, 3H), 1.36 (m, 6H), 2.77 (m, 1H), 2.97 (m, 1H), 3,51 (br, 1H), 3.81 (m, 1H), 4.50 (dd, 1H), 7.39 (m, 5H).

36.3 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide

[0153] N,N-Diisopropyl-3-cyano-3-phenylpropanamide (21.1 g, 82 mmol) was dissolved in EtOH (130 mL) and 2 M NaOH (100 mL). Hydrogen peroxide (30%, 20.2 mL, 200 mmol) was added and the mixture was stirred at ambient temperature for two hours. The resulting precipitate was filtered, washed with water and dried, yielding the title compound as white crystals, 15.6 g (69%): ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.19 (d, 3H), 1.31 (m, 6H), 2.51 (dd, 1H), 3.30 (dd, 1H), 3.41 (m, 1H), 4.02 (m, 1H), 4.18 (dd, 1H), 5.7 (br, 1H), 6.4 (br, 1H), 7.21-7.42 (m, 5H).

36.4 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide

[0154] N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide was treated as described in Example 34:3 (two days of reflux and no chromatography) which gave the title compound as a colourless semicrystalline oil, 15.9 g (93%): ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 9H), 1.36 (m, 6H), 2.53 (dd, 1H), 3.18 (dd, 1H), 3.4 (br, 1H), 3.98 (m, 1H), 4.15 (m, 3H), 7.31 (m, 5H).

36.5 N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide

[0155] The method described for Example 35 above was used, starting from N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide. The crude was chromatographed on silica (petroleum ether-EtOAc, 3:2), affording the title compound as a light yellow oil, 0.77 g (46%): ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H), 1.14 (d, 3H), 1.29 (m, 6H), 2.98 (m, 2H), 3.4 (br, 1H), 3,93 (m, 1H), 4.79 (t, 1H), 6.82 (s, 1H), 7.28 (m, 5H), 7.76 (s, 1H).

EXAMPLE 37

N,N-Diisopropyl-3-(oxazol-2-yl)-3-phenylpropanamine hydrochloride

[0156] A mixture of N,N-diisopropyl-3-carbamoyl-3-phenylpropanamine, prepared in Example 34.2 (4.05 g, 15.4 mmol), 1,2-dichloroethyl ethyl ether (2,32 g, 16.2 mmol), water (0.300 g, 16.6 mmol) and formic acid (50 mL) was stirred at 75°C for 3 hours. The formic acid was evaporated and the residue was dissolved in water/diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine 97:3). The pure amine was precipitated as hydrochloride salt with HCl-saturated diethyl ether, affording the title compound as white crystals, 0.61 g (12%): mp 157-158°C; ^{1}H NMR (DMSO(d_6)) δ 1.11 (m, 12H), 2.35 (m, 1H), 2.63 (m, 1H), 3.03 (m, 2H), 3.56 (m, 2H), 4.45 (m, 1H), 7.21-7.40 (m, 6H) 8.06 (d, 1H), 10.20 (br, 1H).

EXAMPLE 38

N,N-Diisopropyl-3-phenyl-3-(thiazol-2-yl)propanamine hydrochloride

[0157] The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine (1.11 g, 4.0 mmol) yielded white crystals of the title compound, 1.12 g (82%): mp 155-156°C; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 12H), 2.75-3.15 (m, 4H), 3.60 (m, 2H), 4.45 (t, 1H), 7.25-7.36 (m, 6H), 7.71 (d, 1H), 11.30 (br, 1H).

[0158] The starting compound N,N-diisopropyl-3-phenyl-3-thiocarbamoylpropanamine was prepared as follows:

38.1 N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine

[0159] H_2S was bubbled into a solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine, prepared in Example 34.1, (3.45 g, 14.3 mmol) and triethylamine (2.0 g, 20 mmol) in dry pyridine (10 mL) until saturation was achieved. The stirred reaction was held under H_2S-atmosphere at 65°C for 5 days. The pyridine was evaporated and the crude product was chromatographed on silica (chloroform-methanol-conc. ammonia 380:20:1), yielding the title compound as a colourless glassy oil, 3.1 g (78%): ^{1}H NMR ($CDCl_3$) δ 0.99 (m, 12H), 2.07 (m, 1H), 2.40 (m, 3H), 3.05 (m, 2H), 4.10 (t, 1H), 7.20-7.45 (m 5H), 7.7-8.1 (b, 1H), 8.0-8.5 (br, 1H).

EXAMPLE 39

N,N-Diisopropyl-3-(4-methylthiazol-2-yl)-3-phenylpropanamine hydrochloride

[0160] The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine, prepared in Example 38.1, (1.5 g, 5,4 mmol), and 2-chloroacetone (0.75 g, 8.1 mmol) yielded the title compound as a white amorphous substance, 1.1 g (56%): mp 178-181°C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 12H), 2.50 (s, 3H), 2.98 (m, 3H), 3.18 (m, 1H), 3.60 (m, 2H), 6.94 (d, 1H), 7.30-7.47 (m, 5H), 11.15 (br, 1H).

EXAMPLE 40

N,N-Diisopropyl-3-(thiazol-5-yl)-3-phenylpropanamine hydrochloride

[0161] The title compound was prepared in an analogous manner to that described in Example 35. Reaction with N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine (1.14 g, 3.7 mmol) gave a crude that was chromatographed on silica (petroleum ether-triethylamine 97:3), affording white crystals of the title compound, 0.19 g (30%): mp 193-194°C; ^{1}H NMR ($CDCl_3$) δ 1.1.34 (m, 12H), 2.85 (m, 4H), 5.56 (m, 2H), 4.29 (t, 1H), 7.26-7.39 (m, 5H), 7.73 (s, 1H), 8.71 (s, 1H) 11.61 (br, 1H).

[0162] The starting compound N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine was prepared as

follows:

40.1 N,N-Diisopropyl-3-ethoxythiocarbonyl-3-phenylpropanamine

[0163] HCl-gas was bubbled through an ice-cold solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine (2.9 g, 12 mmol), prepared in Example 34.1, in dried ethanol (50 mL, molecular sieve 3 Å) until saturation. The stirred reaction was held under HCl-atmosphere at room temperature overnight. The solvent was carefully evaporated and the remaining oil was dissolved in dry pyridine (100 mL). To this solution was added triethylamine (5.7 g, 56 mmol) and to the now thick suspension was bubbled H_2S until saturation was achieved. The dark olive-green reaction mixture was held under a H_2S-atmosphere at 65°C overnight. The solvent was evaporated and the residue was partioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 198:1:1), affording the title compound as a straw-coloured liquid, 1.24 g (33%): ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 12H), 1.34 (t, 2H), 1.97 (m, 1H), 2.37 (m, 3H), 2.98 (m, 2H), 4.10 (t, 1H) 4.46 (m, 2H), 7.13-7.39 (m, 5H).

EXAMPLE 41

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl) - propanamine fumarate

[0164] To a suspension of lithium aluminium hydride (LAH) (0.51 g 13.3 mmol) in THF (30 mL), N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide (2.0 g, 5.33 mmol) was added and warmed to 50°C overnight. The reaction mixture was quenched and the solvent was evaporated. The residue was dissolved in diethyl ether and extracted twice with 2 M HCl, and the combined aqueous phases were washed twice with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted three times with diethyl ether, the combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent evaporated. The pure amine was crystallised from methanol as its fumarate, yielding the title compound as white crystals, 1.52 g (58%): mp 203-205°C; ^{1}H NMR (DMSO) δ 1.00 (d, 12H), 2.02 (q, 2H), 2.33 (m, 2H), 3.18 (m 2H), 4,62 (t, 1H), 6.50 (s, 1H), 6.68-7.18 (m, 6H), 7.28 (t, 1H).

[0165] The starting compound N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide was prepared as follows:

41.1 N,N-Diisopropyl-3-(2-thienyl)propenamide

[0166] 2-Bromothiophene (2.28 g, 14.0 mmol), N,N-diisopropylacrylamide (1.55 g, 10.0 mmol), palladium(II)acetate (34 mg, 0.15 mmol), tri-o-tolylphosphine (183 mg, 0.6 mmol), tri-n-butyl amine (2.04 g, 11.0 mmol) and dry DMF (5 mL) were mixed under a N_2-atmosphere. The mixture was heated to 130°C for 9 hours. Diethyl ether and H_2O was added to the somewhat cooled mixture. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed twice with 2 M HCl, once with water, once with brine, and dried ($MgSO_4$), and the solvent was then evaporated. The crude product was chromatographed on silica (petroleum ether-ethyl acetate 4:1), affording a yellow oil, 1.58 g (66%): ^{1}H NMR ($CDCl_3$) δ 1.35 (br, 12H), 3.9 (br, 1H), 4.1 (br 1H), 6.65 (d, 1H), 7.00-7.30 (m, 3H), 7.72 (d, 1H).

41.2 2-Methoxyphenyllithium

[0167] 2-Methoxybromobenzene (8.44 g 45.1 mmol) was dissolved in dry diethyl ether (15 mL). The mixture was cooled to -78°C. n-BuLi (17.8 mL, 45.0 mmol) was added and the mixture was stirred for one hour at -78°C and then for 20 min. at -10°C. The aryl lithium solution was used immediately.

41.3 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide

[0168] Copper(I)bromide dimethyl sulfide complex (4.63 g 22.5 mmol) was dissolved in dimethyl sulfide (18 mL), and diethyl ether (15 mL). The solution was cooled to 0°C, whereafter 2-methoxyphenyllithium (41.2) (45 mmol) was added. After 10 min., the temperature was lowered to -78°C. Trimethylsilylchloride (4.89 g, 45.0 mmol) was added, followed by N,N-diisopropyl-3-(2-thienyl)propenamide (41.1) (3.56 g, 15 mmol) in diethyl ether (20 mL). The temperature was allowed to slowly rise to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and conc. ammonia (10 mL). Diethyl ether (80 mL) was added and the mixture was filtered through Celite. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed once with brine and dried ($MgSO_4$). The solvent was evaporated and the crude product was chromatographed on silica (petroleum ether-ethyl

acetate 3:1), affording a yellow oil, 3.75 g (73%): ^{1}H NMR ($CDCl_3$) d 1.12 (t, 6H), 1.29 (t, 6H), 3.02 (m, 2H), 3.4 (br, 1H), 3.80 (s, 3H), 4.03 (m, 1H), 5.26 (t, 1H), 6.8-7.3 (m, 7H).

41.4 N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide

[0169] A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide (2.37 g, 6.9 mmol) in dichloromethane(35 mL) was cooled down to -78°C and boron tribromide (5.9 g 23.57 mmol) was added. The reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched by slow addition of water (20 mL). The pH was adjusted to around 6 with $NaHCO_3$(s) and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent was evaporated. This crude product (2.46 g, 107%) was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.20 (m, 6H), 1.35 (d, 3H), 3.16 (m, 2H), 3.4 (br, 1H), 4.0 (m, 1H), 5.24 (dd. 1H), 6.7-7.2 (m, 7H).

[0170] Examples 42-54 and 57 and 58 were prepared with the methodology described for Example 41, starting with the appropriate acrylamides and aryl bromides.

EXAMPLE 42

N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-(2-thienyl)propanamine

[0171] The crude product was crystallised from petroleum ether/ethyl acetate affording the title compound, 0.41 g as slightly pink crystals: mp 102-109°C; ^{1}H NMR ($CDCl_3$) δ 1.11 (m, 12H), 2.01 (m, 1H), 2.41 (m, 2H), 2.72 (m, 1H), 3.26 (m, 2H), 4.66 (dd, 1H), 6.30 (dd, 1H), 6.45 (d, 1H), 6.73 (d, 1H), 6.91-7.00 (m, 2H), 7.17 (dd, 1H).

EXAMPLE 43

N,N-Diisopropylamine-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine, fumarate

[0172] White crystals, 0.95 g: mp 153-155°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 2H), 3.05 (m, 2H), 3.68 (m, 2H), 3.85 (s, 3H), 4.71 (t, 1H), 6.68 (s, 2H), 6.89-7.03 (m, 4H), 7.20-7.30 (m, 3H).

EXAMPLE 44

N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-(2-thienyl)propanamine fumarate

[0173] White crystals, 1.52 g: mp 103-109°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.46 (m, 2H), 3.04 (m, 2H), 3.66 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.60 (t, 1H), 6.46-6.58 (m, 2H), 6.68 (s, 2H), 6.91-6.97 (m, 2H), 7.09- 7.26 (m, 2H).

EXAMPLE 45

N,N-Diisopropyl-3-(3-methoxyphenyl)-3-(2-thienyl)propanamine hydrochloride

[0174] White crystals, 1.16 g: mp 95-97°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.49 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.68 (m, 2H), 3.77 (s, 3H), 4.31 (t, 1H), 6.83 (m, 1H), 6.68-7.02 (m, 4H), 7.27 (m, 2H).

EXAMPLE 46

N,N-Diisopropyl-3-(4-methoxyphenyl)-3-(2-thienyl) - propanamine hydrochloride

[0175] White amorphous substance, 0.50 g: mp 157-160°C; ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.47 (m, 2H), 2.94 (m, 1H), 3.12 (m, 1H) 3.68 (br, 2H), 3.77 (s, 3H), 4.28 (t, 1H), 6.87-7.00 (m, 4H), 7.23-7.32 (m, 3H).

EXAMPLE 47

N-Isopropyl-N-methyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine fumarate

[0176] White crystals, 1.32 g: mp 141-143°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.50 (m, 2H), 2.73 (s, 3H), 3.04 (m, 2H), 3.58 (m, 1H), 3.84 (s, 3H), 4.73 (t, 1H), 6.68 (s, 2H), 6.96 (m, 4H), 7.24 (m, 3H).

EXAMPLE 48

N,N-Diisopropyl-3-phenyl-3-(2-thienyl)propanamine, hydrochloride

[0177] White crystals, 0.74 g: mp 165-166°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.52 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.70 (br, 2H), 4.34 (t, 2H), 6.92-7.04 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 49

N-Cyclohexyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

[0178] White crystals, 1.1 g: mp 197-199°C; ^{1}H NMR (CD_3OD) δ 1.15-1.52 (br, 5H), 1.68 (br, 1H), 1.90 (br, 4H), 2.51 (br, 2H), 2.78 (s, 3H), 2.91-3.40 (m, 3H), 4.31 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 50

N,N-Diethyl-3-phenyl-3-(2-thienyl)propanamine fumarate

[0179] White crystals, 1.7 g (tot. 49 %): mp 135-137°C; ^{1}H NMR (CD_3OD) δ 1.22 (t, 3H), 2.50 (m, 2H), 2.90-3.26 (m, 6H), 4.30 (t, 1H), 6.68 (s, 2H), 6.92-7.03 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 51

N-Isopropyl-N-methyl-3-phenyl-3-(2-thienyl)propanaminehydrochloride

[0180] White crystals, 1.6 g: mp 139-144°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.52 (m, 2H), 2.75 (s, 3H), 3.03 (m, 2H), 3.59 (m, 1H), 4.32 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 52

N-[3-Phenyl-3-(2-thienyl)propyl]pyrrolidine fumarate

[0181] Crystallisation from 2-propanol, 1.1 g: mp 144-145°C; ^{1}H NMR (CD_3OD) δ 2.02 (m, 4H) 2.31 (m, 2H), 2.97-3.42 (m, 6H), 4.29 (t, 1H), 6.69 (s, 2H), 6.91-7.01 (m, 2H), 7.18-7.38 (m, 6H).

EXAMPLE 53

N-[3-Phenyl-3-(2-thienyl)propyl]piperidine hydrochloride

[0182] The hydrochloride was crystallised from ethylmethylketone, 0.84 g: mp 193-194°C; ^{1}H NMR (CD_3OD) δ 1.40-2.00 (b, 6H), 2.54 (m, 2H), 2.82-3.80 (m, 6H), 4.29 (t, 1H), 6.91-7.03 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 54

N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine hydrochloride

[0183] White crystals, 2.1 g: mp 205-210°C; ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 12H), 2.18 (s, 3H), 2.63 (m, 2H), 2.95 (m, 2H), 3.54 (m, 4H), 4.61 (t, 1H), 6.76-7.01 (m, 5H), 7.16 (d, 1H).

EXAMPLE 55

(R*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

[0184] To the racemic free base of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-2-thienylpropanamine (20 g, 0.06 mol), prepared in Example 54, in abs. ethanol (50 g) was added L-(+)-tartaric acid (9.5 g 0.063 mol) in ethanol (60 g). The salt formed was filtered off and crystallised twice from ethanol/methanol 10/1, 10 mL per gram of crystals, affording the title compound as white crystals, (6.8 g, 14.1 mmol): mp 214-215°C; $[\alpha]_{Hg}$=+17.3° (c=3.82 in methanol).

EXAMPLE 56

(S*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

[0185] From the mother liquid from the first crystallisation to obtain (R*) N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine in Example 55, the free base was recovered. The amine was treated with a 5% excess of D-(-)-tartaric acid in ethanol as above, yielding the title compound as white crystals, 6.1 g (12.7 mmol): mp 214°C; $[\alpha]_{Hg}$=-17.5° (c=3.85 in methanol).

EXAMPLE 57

N,N-Diisopropyl-3-phenyl-3-(3-thienyl)propanamine hydrochloride

[0186] White crystals, 0.94 g: mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 12H), 2.87 (m, 4H), 3.56 (br, 2H), 3.98 (t, 1H), 6.94 (dd, 1H), 7.27 (m, 7H), 11.4 (br, 1H).

[0187] The starting compound was prepared as follows:

57.1 N,N-Diisopropyl-3-(3-thienyl)propenamide

[0188] Sodium hydride, 60% in mineral oil (3.9 g, 98 mmol), was washed several times with petroleum ether and dried under a stream of nitrogen. Sodium-dried THF was added followed by diethyl N,N-diisopropyl acetamidephosphonate (27.4 g, 98 mmol). When the evolution of gas had ceased, thiophene-3-aldehyde (10.0 g, 89.2 mmol) in THF (50 mL) was added at such a rate that the temperature never exceeded 45°C. After one hour of stirring at ambient temperature, the reaction was quenched with 4 mL of water and stirred for another hour. The solvent was evaporated and the residue was taken up in diethyl ether/2M NaOH. The organic phase was washed once with water and once with brine, dried (Na_2SO_4) and evaporated. The crude was chromatographed on silica (petroleum ether-ethyl acetate 4:1) affording the title compound as a light-brown oil, 14.8 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.37 (b, 12H), 3.86 (br, 1H), 4.10 (br, 1H), 6.68 (d, 1H), 7.27-7.41 (m, 3H), 7.59 (d, 1H).

EXAMPLE 58

N,N-Diisopropyl-3-(2-furanyl)-3-phenylpropanamine hydrochloride

[0189] White crystals, 60 mg: mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (br, 12H), 2.64 (m, 1H), 2.85 (m, 3H), 3.55 (m, 2H), 3.98 (t, 1H), 6.16 (d, 1H), 6.31 (dd, 1H), 7.30 (m, 6H), 11.4 (br, 1H).

[0190] The starting compound was prepared as follows:

58.1 N,N-Diisopropyl-3-(2-furanyl)propenamide

[0191] The title compound was obtained from furfural with the procedure described in Example 57.1, as a colourless oil, 11.2 g (75%): ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 12H), 4.0 (br, 2H), 6.41 (m, 2H), 6.76 (d, 1H), 7.38 (m, 2H).

EXAMPLE 59

N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl - propanamine fumarate

[0192] A solution of N,N-diisopropyl-3-(N-methyl-pyrr-2-yl)-3-phenyl-propanamide (4.92 g, 15.7 mmol) in THF (75 mL), was dropped into a stirred mixture of LAH (2.38 g, 62.8 mmol). Stirring was continued at 50 °C overnight. Standard work-up gave the amine as a yellow oil, which was isolated as the fumarate salt, 2.74 g (42 %): m.p. 134-6°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 6H), 1.29 (d, 6H), 2.24 (m, 1H), 2.48 (m, 1H), 2.97 (dt, 1H), 3.26 (dt, 1H), 3,32 (s, 3H), 3.69 (septet, 2H), 4.08 (t, 1H), 6.05 (t, 1H), 6.16 (m, 1H), 6.57 (dd, 1H), 6.71 (s, 2H) and 7.19-7.34 (m, 5H).

[0193] The starting compound was prepared as follows:

59.1 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide

[0194] The title compound was prepared from N-methyl-2-pyrrolaldehyde and N,N-diisopropyl-dimethylphosphon acetamide analogously to Example 4.2, giving 7.61 g (92%): ^{1}H NMR($CDCl_3$) δ 1.32 (d, 6H), 1.35 (d, 6H), 3.68 (s, 3H), 4.00 (m, 2H), 6.13 (t, 1H), 6.55-6.66 (3H) and 7,57 (d, 1H).

59.2 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl - propanamide

[0195] The title compound was prepared from N,N-diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide by a method analogous to that described in Example 41.3, giving 4.92 g (78 %): ^{1}H NMR ($CDCl_3$) δ 0.85-1.32 (4d from rotamers, 12H), 2.91 (d, 2H), 3.31 (s, 3H) 3.45 (m, 1H), 3.88 (m, 1H), 4.65 (t, 1H), 6.07 (2H), 6.50 (dd, 1H) and 7.15-7.22 (5H).

EXAMPLE 60

3-(N-Methylpyrrol-2-yl)-3-phenyl-1-pyrrolidinopropane fumarate

[0196] The title compound was prepared analogously to Example 59, using N,N-tetramethylene-dimethylphosphon acetamide, yield 950 mg (36 % tot.): m.p. 194-5°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 12H), 2.2-2.6 (m, 2H) 3.05 (m, 2H), 3.66 (sept., 2H), 4.03 (t, 1H), 6.02 (two d, 2H), 6.64 (t, 1H), 6.69 (s, 2H) and 7.28 (m, 5H).

BIOLOGICAL EVALUATION

[0197] The pharmacological activity of compounds prepared in the Examples was tested using in vitro methods.

Functional in vitro studies

[0198] Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilise for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilisation period.

[0199] Carbachol (carbamylcholine chloride) was used as the standard muscarinic receptor agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by two consecutive additions of a submaximal concentration (3 x 10^{-6} M) of carbachol. A concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}- values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1) (Schild, H.I., Br. J. Pharmacol. Chemother. 1949, 4, 277-280), where [A] is the concentration of test compound:

$$K_B = [A]/r-1 \quad (1)$$

[0200] The KB values obtained are presented in Table 1 below.

Table 1

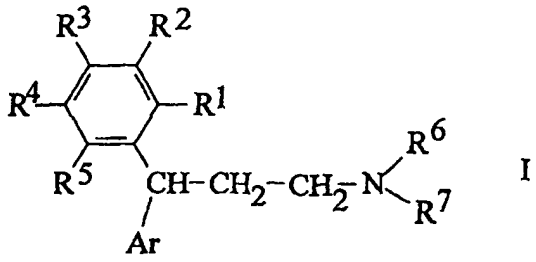
Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
1	499	23	1.05	45	51
3	236	24	1.91	46	286
4	132	27	7.1	47	91
5	336	28	8.55	48	31
6	10	29	1.5	49	590
7	13	30	139	50	154
8	26	31	14	51	118
9	3.8	32	36	52	350
10	171	33	56	53	154

Table 1 (continued)

Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
11	431	34	803	55	2
12	1.18	35	1773	56	360
13	15	36	2640	59	690
14	4.5	37	520	60	707
15	15	38	207		
16	32	39	235		
17	3.5	40	814		
18	172	41	7.6		
19	2.9	42	286		
20	3315	43	29		
22	2.8	44	2285		

Claims

1. A compound of Formula (I):



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,
R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,
R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, alkoxycarbonylalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl having at least two carbon atoms, alkoxy having at least two carbon atoms, hydroxyalkyl having at least two carbon atoms,
R^5 is hydrogen, halogen, alkyl,
Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and
R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen;
with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or
(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or
(iii) Ar is heteroaryl, or
(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then

R^4 may also be hydrogen, methyl, methoxy, hydroxymethyl, hydroxy, halogen, carbamoyl, sulphamoyl;
and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;
their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. The compound according to claim 1, wherein R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

3. The compound according to claim 2, wherein R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

4. The compound according to claim 1, wherein Ar is heteroaryl.

5. The compound according to claim 4, wherein R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

6. The compound according to claim 1, wherein R^1 is hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen, and Ar is other than phenyl that is ortho-substituted by hydroxy or alkoxy.

7. The compound according to claim 6, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

8. The compound according to claim 1, wherein at least one of R^6 and R^7 is aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom in at least one position.

9. The compound according to claim 8, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

10. The compound according to any one of claims 1 to 9, wherein R^1 is hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

11. The compound according to any one of claims 1 to 10, wherein R^2 and R^3 independently are hydrogen, hydroxy or hydroxymethyl.

12. The compound according to any one of claims 1 to 10, wherein R^4 is hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyi, amino, azido, cyanoalkyl, carboxy or carboxyalkyl.

13. The compound according to claim 12, wherein R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethylaminoethyl.

14. The compound according to any one of claims 1 to 13, wherein R^5 is hydrogen.

15. The compound according to any one of claims 1 to 14, wherein each of R^6 and R^7 independently signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group such as C_{1-8}alkyl, especially C_{1-6}alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms.

16. The compound according to any one of claims 1 to 14, wherein R^6 and R^7 taken together form a ring with the

amine nitrogen.

17. The compound according to any one of claims 1 to 16, wherein at least one of R^6 and R^7 comprises a branched carbon chain.

18. The compound according to any one of claims 1 to 17, wherein Ar is thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl or methylpyrryl.

19. The compound according to claim 1, which is:

N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride,
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine, or its 3(R)-isomer,
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its 1(S*)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamine, or its (R)-isomer,
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine,
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine, or
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, or its (R)-isomer.

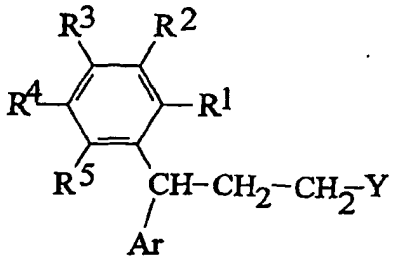
20. The compound according to any one of claims 1 to 19 for use as a pharmaceutically active substance, especially as an anticholinergic agent.

21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19, and preferably a compatible pharmaceutical carrier.

22. Use of a compound according to any one of claims 1 to 19 for preparing an anticholinergic drug.

23. A method of preparing a compound according to any one of claims 1 to 19, which comprises:

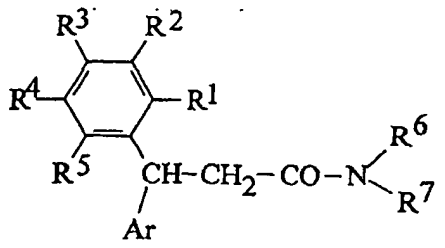
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined in claim 1, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

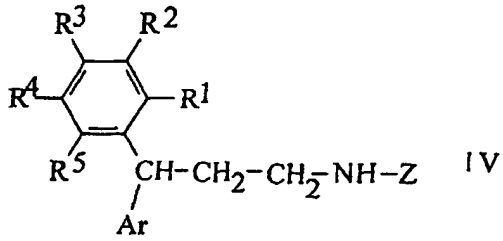
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, or

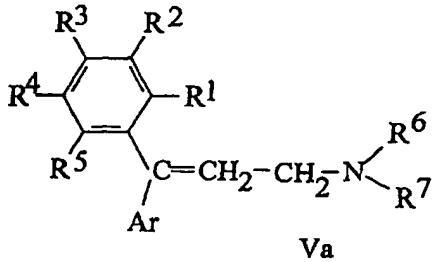
c) N-alkylating a secondary amine of Formula IV



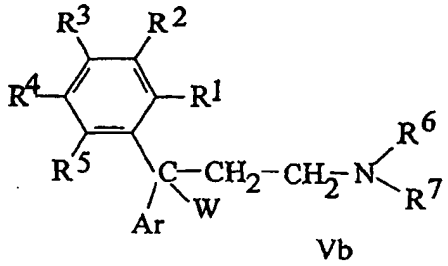
IV

wherein R^1 to R^5 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



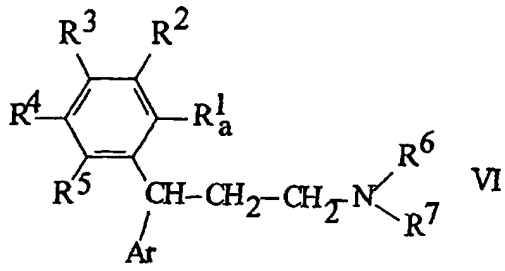
Va



Vb

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

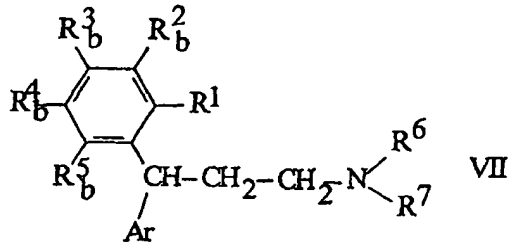
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined in claim 1, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

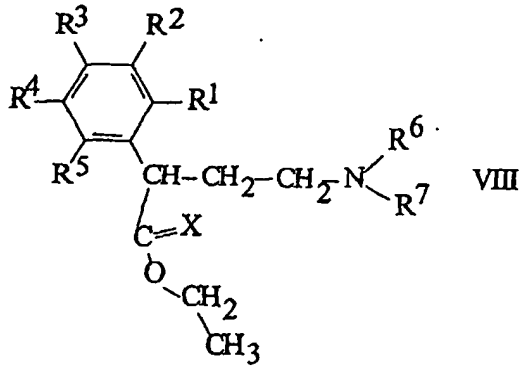


VII

wherein R^1, R^6, R^7 and Ar are as defined in claim 1, and one of R^2b to R^5b is alkylene and the others are as defined in claim 1 for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined in claim 1, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

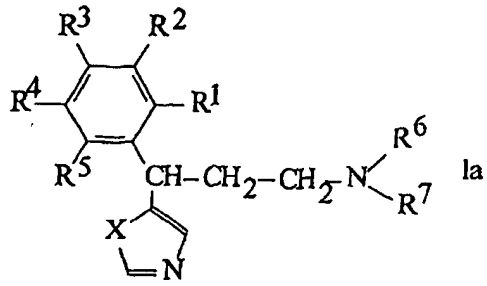


VIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, with a compound of Formula IX

$CH_3N=C$: IX

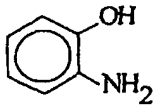
to form a compound of Formula Ia



Ia

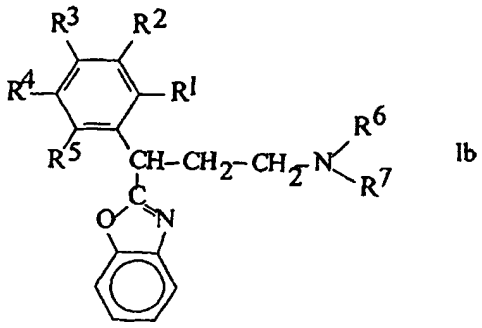
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

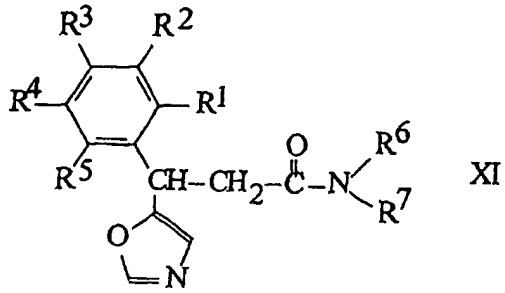
to form a compound of Formula Ib



Ib

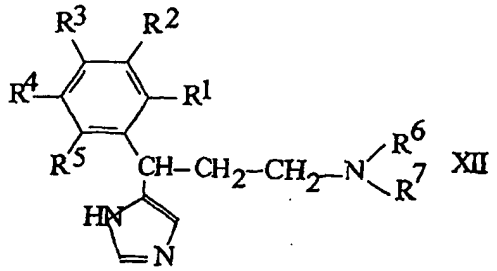
wherein R^1 to R^7 are as defined in claim 1, or

j) converting a compound of Formula XI



XI

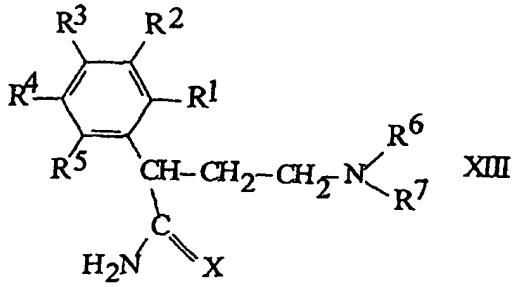
wherein R^1 to R^7 are as defined in claim 1, to a compound of Formula XII



XII

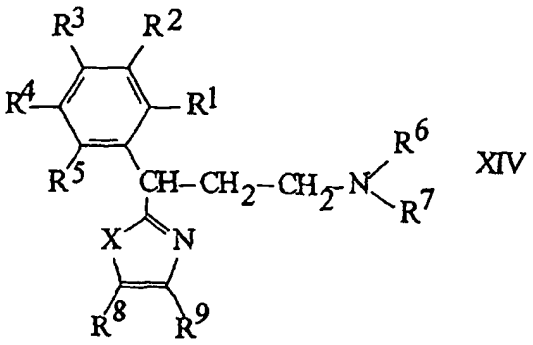
wherein R^1 to R^7 are as defined in claim 1, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, to a compound of Formula XIV



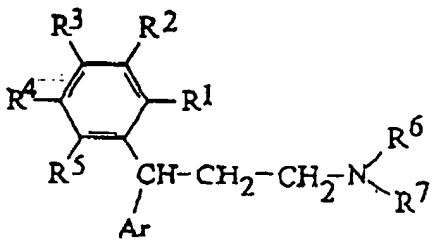
XIV

wherein R^1 to R^7 and X are as defined above, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,
ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

Patentansprüche

1. Eine Verbindung der Formel (I);



worin:

R^1 Wasserstoff, Hydroxyl, Alkyl, Alkoxy, Hydroxyalkyl, Trifluormethyl, Amino, Alkylcarbonylamino, Alkylcarbonyloxy, Halogen ist,

R^2 und R^3 unabhängig voneinander Wasserstoff, Hydroxy, Alkyl, Alkoxy, Hydroxyalkyl, Halogen, Alkoxycarbonylalkyl, Carbamoyl, Sulfamoyl sind,

R^4 ω-Hydroxyalkoxy, ω-Aminoalkoxy, ω-Aminoalkylamino, Alkoxyalkyl, Hydroxyalkoxyalkylaminoalkyl, Alkoxycarbonylalkyl, Dihydroxyalkyl, Formyl, Alkylcarbonyl, Alkoxycarbonylalkyl, Alkylcarbonylaminoalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Carbamoylalkyl, Carboxamidoalkyl, Carboxyl, Amino, Nitro, Cyano, Nitrilo, Cyanoalkyl, Azido, Alkyl mit wenigstens zwei Kohlenstoffatomen, Alkoxy mit wenigstens zwei Kohlenstoffatomen, Hydroxyalkyl mit wenigstens zwei Kohlenstoffatomen ist,

R^5 Wasserstoff, Halogen, Alkyl ist,

Ar Aryl oder Heteroaryl ist, welches mono- oder unabhängig disubstituiert sein kann mit Alkyl, Alkoxy, Hydroxy, Hydroxyalkyl, Halogen, Alkoxycarbonylalkyl, Carbamoyl, Sulfamoyl, und

R^6 und R^7 Hydrocarbylgruppen sind, welche gleich oder verschieden sein können, die zusammen wenigstens

drei Kohlenstoffatome enthalten und welche eine oder mehrere Hydroxygruppen tragen können, und wobei die Kohlenstoffatome durch Sauerstoffatome miteinander verbunden sein können und wobei R^6 und R^7 zusammen mit dem Aminstickstoff einen Ring bilden können; unter den Vorbehalten, dass (a) wenn:

(i) wenigstens zwei von R^2, R^3 und R^5 von Wasserstoff verschieden sind oder

(ii) R^1 von Hydroxy oder Methoxy verschieden ist und Ar von Phenyl, das durch Hydroxy oder Methoxy ortho-substituiert ist, verschieden ist oder

(iii) Ar Heteroaryl ist oder

(iv) wenigstens einer von R^6 und R^7 ein aromatisches Hydrocarbyl oder Cycloalkyl ist, dann

R^4 ebenfalls Wasserstoff, Methyl, Methoxy, Hydroxymethyl, Hydroxy, Halogen, Carbamoyl, Sulfamoyl sein kann;
und (b) wenn Ar ein unsubstituiertes Phenyl ist, dann R^1, R^2, R^3, R^4 und R^5 nicht alle Wasserstoff sein können;

deren Salze mit physiologisch verträglichen Säuren und, wenn die Verbindungen in Form von optischen Isomeren vorliegen können, die racemische Mischung der einzelnen Enantiomere.

2. Die Verbindung gemäß Anspruch 1, wobei R^4 ω-Hydroxyalkoxy, ω-Aminoalkoxy, ω-Aminoalkylamino, Alkoxyalkyl, Hydroxyalkoxyalkylaminoalkyl, Dihydroxyalkyl, Formyl, Alkylcarbonyl, Alkoxycarbonyl, Alkoxycarbonylalkyl, Alkylcarbonylaminoalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Carbamoylalkyl, Carboxamidoalkyl, Carboxyl, Amino, Nitro, Cyano, Nitrilo, Cyanoalkyl oder Azido ist.

3. Die Verbindung gemäß Anspruch 2, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind, und Ar Phenyl oder Phenyl, welches mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

4. Die Verbindung gemäß Anspruch 1, wobei Ar Heteroaryl ist.

5. Die Verbindung gemäß Anspruch 4, wobei R^1 Wasserstoff oder Methyl ist und R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind.

6. Die Verbindung gemäß Anspruch 1, wobei R^1 Wasserstoff, Alkyl, Hydroxyalkyl, Trifluormethyl, Amino, Alkylcarbonylamino, Alkylcarbonyloxy oder Halogen ist und Ar von Phenyl, das durch Hydroxy oder Alkoxy ortho-substituiert ist, verschieden ist.

7. Die Verbindung gemäß Anspruch 6, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind, und Ar Phenyl oder Phenyl, welches mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

8. Die Verbindung gemäß Anspruch 1, wobei wenigstens einer von R^6 und R^7 ein aromatisches Hydrocarbyl, Cydoalkyl oder eine Hydrocarbylkette ist, wobei die Kohlenstoffatome über ein Sauerstoffatom in wenigstens einer Position miteinander verbunden sind.

9. Die Verbindung gemäß Anspruch 8, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen WasserStoff sind, und Ar Phenyl oder Phenyl, das mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

10. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 9, wobei R^1 Hydroxy, Halogen, Trifluormethyl, Amino, Methoxy oder Hydroxymethyl ist

11. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 10, wobei R^2 und R^3 unabhängig voneinander Wasser-

stoff, Hydroxy oder Hydroxymethyl sind.

12. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 10, wobei R^4 WasserStoff, Formyl, Alkoxycarbonyl, Alkylcarbonyl, Hydroxyalkyl, Alkoxyalkyl, Carboxamidoalkyl, Carbamoylalkyl, Aminoalkyl, Amino, Azido, Cyanoalkyl, Carboxy oder Carboxyalkyl ist.

13. Die Verbindung gemäß Anspruch 12, wobei R^4 Wasserstoff, Formyl, Hydroxymethyl, Hydroxyethyl, Hydroxypropyl, Hydroxybutyl, Hydroxypentyl, Hydroxyhexyl, Ethoxymethyl, Methoxycarbonyl, Amino, Aminopropyl, Acetyl, 1,2-Hydroxyethyl, Ethylaminomethyl oder Hydroxyethoxyethylaminoethyt ist.

14. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 13, wobei R^5 Wasserstoff ist.

15. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 14, wobei jeder von R^6 und R^7 unabhängig voneinander eine gesättigte Hydrocarbylgruppe, insbesondere eine gesättigte aliphatische Hydrocarbylgruppe wie z. B. ein C_{1-8}-Alkyl, insbesondere ein C_{1-6}-Alkyl, oder Adamantyl bedeutet, wobei R^6 und R^7 zusammen wenigstens drei, vorzugsweise wenigstens vier Kohlenstoffatome enthalten.

16. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 14, wobei R^6 und R^7 zusammengenommen mit dem Aminstickstoff einen Ring bilden.

17. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 16, wobei wenigstens einer von R^6 und R^7 eine verzweigte Kohlenstoffkette umfasst.

18. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 17, wobei Ar Thienyl, Pyrryl, Thiazolyl, Oxazolyl, Methylthiazolyl oder Methylpyrryl ist.

19. Die Verbindung gemäß Anspruch 1, welche

N,N-Diisopropyl-3-(2-fluorphenyl)-3-phenylpropanaminhydrochlorid,
N,N-Diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamin oder dessen 3(R)-Isomer,
N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen 1(S*)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N-Cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamin,
N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamin oder
N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamin oder dessen (R)-Isomer ist.

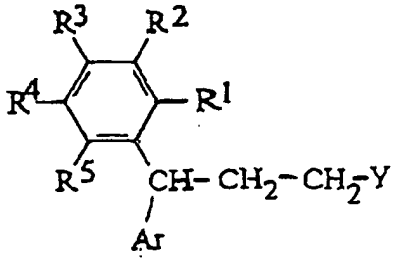
20. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 zur Verwendung als eine pharmazeutisch aktive Substanz, insbesondere als ein anticholinerges Mittel.

21. Eine pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 und vorzugsweise einen kompatiblen pharmazeutischen Träger.

22. Verwendung einer Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 zur Herstellung eines anticholinergen Arzneimittels.

23. Ein Verfahren zur Herstellung einer Verbindung gemäß irgendeinem der Ansprüche 1 bis 19, welches umfasst:

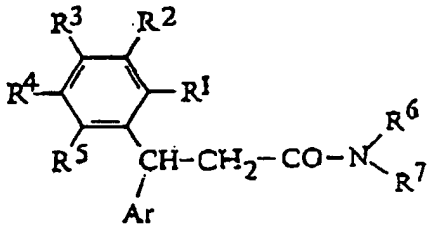
a) Umsetzen einer Verbindung der Formel II



II

worin R^1 bis R^5 und Ar wie in Anspruch 1 definiert sind und Y eine Abgangsgruppe ist, mit einem Amin HNR^6R^7, wobei R^6 und R^7 wie oben definiert sind, oder

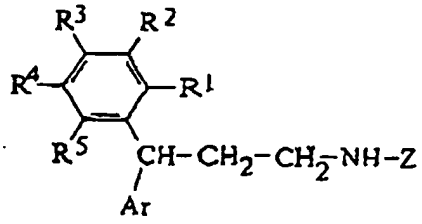
b) Reduzieren einer Verbindung der Formel III



III

worin R^1 bis R^7 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, oder

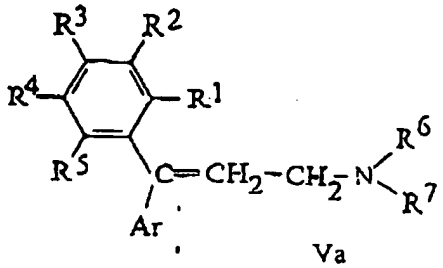
c) N-Alkylieren eines sekundären Amins der Formel IV



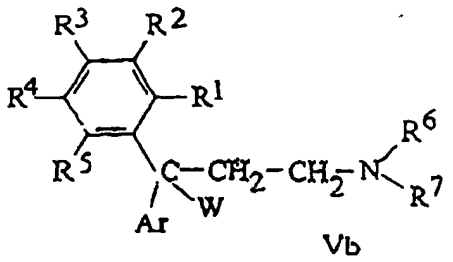
IV

worin R^1 bis R^5 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, und worin Z dieselbe Bedeutung wie R^6 und R^7 aufweist, oder

d) Reduzieren einer Verbindung der Formel Va oder Vb



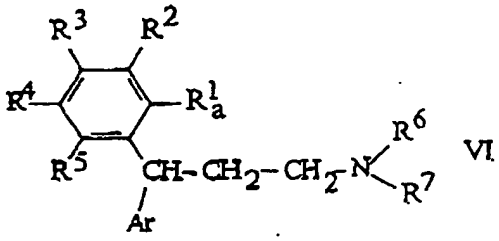
Va



Vb

worin R^1 bis R^7 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, und W eine Hydroxygruppe oder Halogen bedeutet, oder

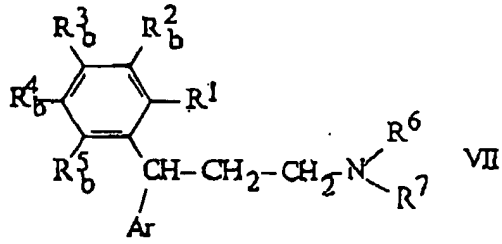
e) bei einer Verbindung der Formel VI



VI

worin R^2 bis R^7 und Ar wie in Anspruch 1 definiert sind und R^1a Carboxyl oder Alkoxy ist, Umwandeln von R^1a in Hydroxy oder

f) bei einer Verbindung der Formel VII

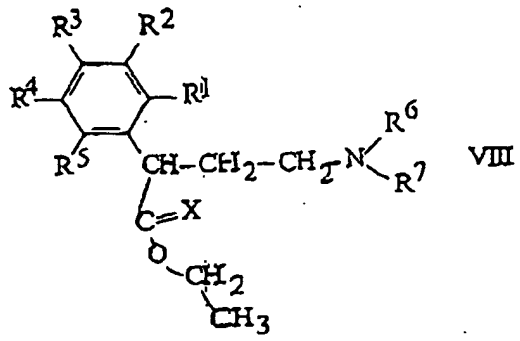


VII

worin R^1, R^6, R^7 und Ar wie in Anspruch 1 definiert sind und einer von $R^2{}_b$ bis $R^5{}_b$ Alkylen ist und die anderen wie in Anspruch 1 wie für R^2 bis R^5 definiert sind, Reduzieren von Alkylen zu Alkyl, Hydroxyalkyl oder Dihydroxyalkyl oder

g) bei einer Verbindung der Formel I wie in Anspruch 1 definiert, Umwandeln von einer oder mehreren der Gruppen R^1 bis R^5 in eine andere oder andere Gruppen R^1 bis R^5 oder

h) Umsetzen einer Verbindung der Formel VIII

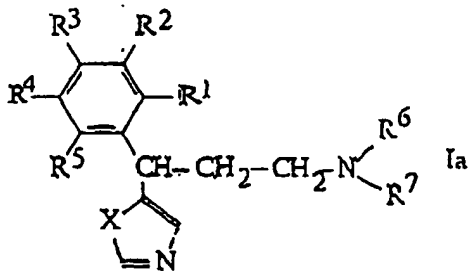


VIII

worin R^1 bis R^7 wie in Anspruch 1 definiert sind und X Sauerstoff oder Schwefel ist, mit einer Verbindung der Formel IX

$$CH_3N{=}C: \qquad \text{IX}$$

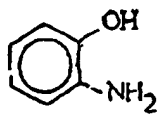
um eine Verbindung der Formel Ia



Ia

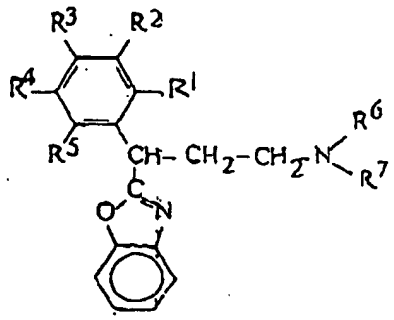
zu bilden, worin R^1 bis R^7 und X wie oben definiert sind, oder

i) Umsetzen einer Verbindung der Formel VIII oben, worin X Sauerstoff ist, mit einer Verbindung der Formet X



X

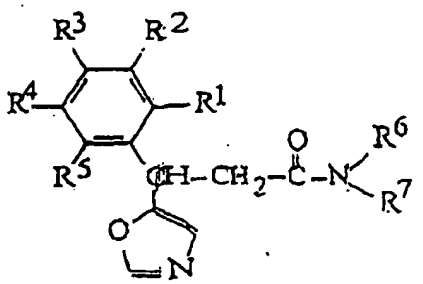
um eine Verbindung der Formel Ib



Ib

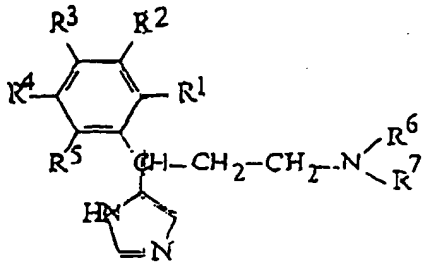
zu bilden, worin R^1 bis R^7 wie in Anspruch 1 definiert sind, oder

j) Umwandeln einer Verbindung der Formel XI



XI

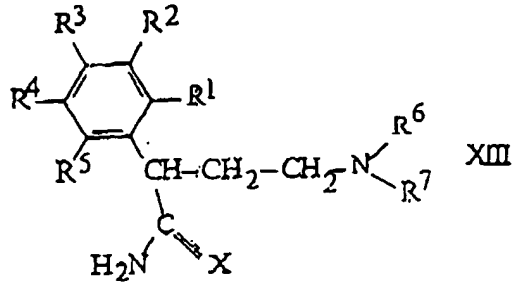
worin R^1 bis R^7 wie in Anspruch 1 definiert sind, in eine Verbindung der Formel XII



XII

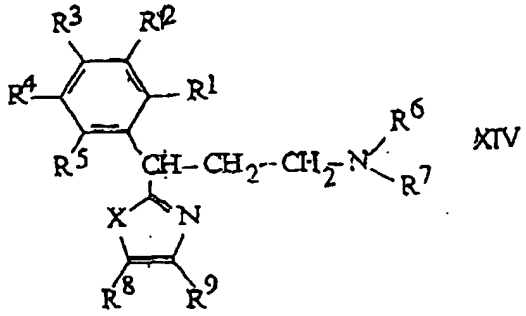
worin R^1 bis R^7 wie in Anspruch 1 definiert sind, oder

k) Umwandeln einer Verbindung der Formel XIII



XIII

worin R^1 bis R^7 wie in Anspruch 1 definiert sind und X Sauerstoff oder Schwefel ist, in eine Verbindung der Formel XIV



XIV

worin R^1 bis R^7 und X wie oben definiert sind und R^8 und R^9 unabhängig voneinander Wasserstoff oder Alkyl sind, und

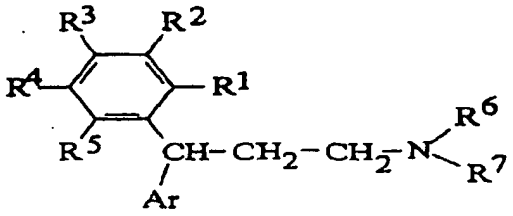
i) wenn nötig, Abspalten der Hydroxyschutzgruppen in den erhaltenen Verbindungen,

ii) wenn gewünscht, Umwandeln der erhaltenen Basen der Formel I in deren Salze mit physiologisch verträglichen Säuren, oder umgekehrt, und/oder

iii) wenn gewünscht, Auftrennen einer erhaltenen Mischung von optischen Isomeren in die einzelnen Enantiomeren.

Revendications

1. Composé de Formule I :



Formule I

dans laquelle :

R^1 est hydrogène, hydroxy, alkyle, alkoxy, hydroxyalkyle, trifluorométhyle, amino, alkylcarbonylamino, alkylcarbonyloxy, halogène,
R^2 et R^3 sont indépendamment hydrogène, hydroxy, alkyle, alkoxy, hydroxyalkyle, halogène, alkoxycarbonylalkyle, carbamoyle, sulphamoyle,
R^4 est ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyle, hydroxyalkoxyalkylaminoalkyle, alkoxycarbonylalkyle, dihydroxyalkyle, formyle, alkylcarbonyle, alkoxycarbonylalkyle, alkylcarbonylaminoalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxylalkyle, carbamoylalkyle, carboxamidoalkyle, carboxyle, amino, nitro, cyano, nitrilo, cyanoalkyle, azido, un alkyle ayant au moins deux atomes de carbone, un alkoxy ayant au moins deux atomes de carbones, un hydroxyalkyle ayant au moins deux atomes de carbones,
R^5 est hydrogène, halogène, alkyle,
Ar est un aryle ou un hétéroaryle pouvant être mono- ou indépendamment di-substitué par un alkyle, alkoxy, hydroxy, hydroxyalkyle, halogène, alkoxycarbonylalkyle, carbamoyle, sulphamoyle, et
R^6 et R^7 sont des groupes hydrocarbyles pouvant être identiques ou différents, contenant ensemble au moins trois atomes de carbone, et pouvant porter un ou plusieurs groupes hydroxy, dans lesquels les atomes de carbones peuvent être interconnectés par des atomes d'oxygène, et dans laquelle R^6 et R^7 peuvent former un cycle avec l'azote aminé ; à la condition que (a) lorsque :

(i) au moins deux des éléments R^2, R^3 et R^5 sont autres qu'hydrogène, ou
(ii) R^1 est autre qu'hydroxy ou méthoxy, et Ar est autre qu'un phényle ortho-substitué par hydroxy ou méthoxy, ou
(iii) Ar est un hétéroaryle, ou
(iv) au moins un des éléments R^6 et R^7 est un cycloalkyle ou un hydrocarbyle aromatique, alors

R^4 peut être hydrogène, méthyle, méthoxy, hydroxyméthyle, hydroxy, halogène, carbamoyle, sulphamoyle;

et à la condition que (b), lorsque :

Ar est un phényle non substitué, alors R^1, R^2, R^3, R^4 et R^5 ne peuvent tous être des atomes d'hydrogène ; leurs sels avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous la forme d'isomères optiques, le mélange racémique et les énantiomères individuels.

2. Composé selon la revendication 1, dans lequel R^4 est ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyle, hydroxyalkoxyalkylaminoalkyle, dihydroxyalkyle, formyle, alkylcarbonyle, alkoxycarbonyle, alkoxycarbonylalkyle, alkylcarbonylaminoalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxylalkyle, carbamoylalkyle, carboxamidoalkyle, carboxyle, amino, nitro, cyano, nitrilo, cyanoalkyle ou azido.

3. Composé selon la revendication 2, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle, ou halogène et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono ou indépendamment disubstitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène.

4. Composé selon la revendication 1, dans lequel Ar est un hétéroaryle.

5. Composé selon la revendication 4 dans lequel R^1 est hydrogène ou méthyle, et soit R^2, R^3, R^4 et R^5 sont tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène.

6. Composé selon la revendication 1, dans lequel R^1 est hydrogène, alkyke, hydroxyalkyle, trifluorométhyle, amino, alkylcarbonylamino, alkylcarbonyloxy ou halogène, et Ar est autre qu'un phényle ortho-substitué par hydroxy ou alkoxy.

7. Composé selon la revendication 6, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3, R^4 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono- ou indépendamment di-substitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou

halogène.

8. Composé selon la revendication 1, dans lequel au moins un des éléments R^6 et R^7 est un cycloalkyle, un hydrocarbyle aromatique ou une chaîne hydrocarbyle dans laquelle les atomes de carbone sont interconnectés par des atomes d'oxygène en au moins une position.

9. Composé selon la revendication 8, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3, R^4 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono- ou indépendamment di-substitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène.

10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel R^1 est hydroxy, halogène, trifluorométhyle, amino, méthoxy ou hydroxyméthyle.

11. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R^2 et R^3 sont indépendamment hydrogène, hydroxy, ou hydroxyméthyle.

12. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R^4 est hydrogène, formyle, alkoxycarbonyle, alkylcarbonyle, hydroxyalkyle, alkoxyalkyle, carboxamidoalkyle, carbamoylalkyle, aminoalkyle, amino, azido, cyanoalkyle, carboxy ou carboxyalkyle.

13. Composé selon la revendication 12, dans lequel R^4 est hydrogène, formyle, hydroxyméthyle, hydroxyéthyle, hydroxypropyle, hydroxybutyle, hydroxypentyle, hydroxyhexyl, éthoxyméthyle, méthoxycarbonyle, amino, aminopropyle, acétyle, 1,2-hydroxyéthyle, éthylaminométhyle, ou hydroxyéthoxy-éthylaminoéthyle.

14. Composé selon l'une quelconque des revendications 1 à 13, dans lequel R^5 est hydrogène.

15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel chacun des éléments R^6 et R^7 désigne indépendamment un groupe hydrocarbyle saturé, en particulier un groupe hydrocarbyle aliphatique saturé tel qu'un alkyle de C_1 à C_8, plus particulièrement un adamantyl ou un alkyle de C_1 à C_6, R^6 et R^7 contenant ensemble au moins trois, de préférence quatre, atomes de carbone.

16. Composé selon l'une quelconque des revendications 1 à 14, dans lequel R^6 et R^7, pris ensemble, forment un cycle avec l'azote aminé.

17. Composé selon l'une quelconque des revendications 1 à 16, dans lequel au moins un des éléments R^6 et R^7 comprend une chaîne de carbone ramifiée.

18. Composé selon l'une quelconque des revendications 1 à 17, dans lequel Ar est thiényl, pyrryl, thiazolyl, oxazolyl, méthylthiazolyl ou méthypyrryl.

19. Composé selon la revendication 1, qui est :

N,N-diisopropyl-3-(2-fluorophényl)-3-phénylpropanamine chlorhydrate,
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(2-hydroxy-5-méthyloxycarbonyl-phényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-acétyl-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyéthyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyéthyl)-phényl]-3-phénylpropanamine, ou son isomère 3 (R),
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyéthyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère 1 (S*),
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyphéxyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-éthoxyméthyl-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(3-acétamidopropyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(2-cyanoéthyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-amino-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),

N,N-diisopropyl-3-(5-azido-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N-cyclobutyl-N-méthyl-3-(2-hydroxyphényl)-3-phénylpropanamine,
N,N-diisopropyl-3-(2-hydroxyphényl)-3-(2-thiényl) propanamine, ou
N,N-diisopropyl-3-(2-hydroxy-5-méthylphényl)-3-(2-thiényl) propanamine, ou son isomère (R).

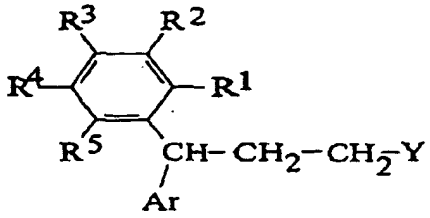
20. Composé selon l'une quelconque des revendications 1 à 19, pour utilisation dans une substance pharmaceutiquement active, en particulier un agent anticholinergique.

21. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 19, et de préférence un véhicule pharmaceutique compatible.

22. Utilisation d'un composé selon l'une quelconque des revendications 1 à 19 pour la préparation d'un médicament anticholinergique.

23. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 19, qui comprend :

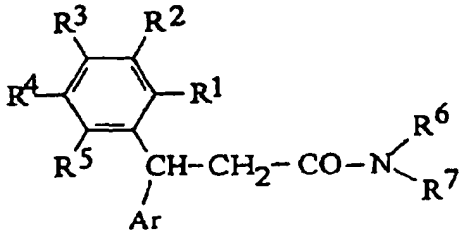
a) la réaction d'un composé de Formule II



Formule II

dans laquelle R^1 à R^5 et Ar sont tels que définis dans la revendication 1, et Y est un groupe partant, avec une amine HNR^6, R^7, dans laquelle R^6 et R^7 sont tels que définis ci-dessus, ou

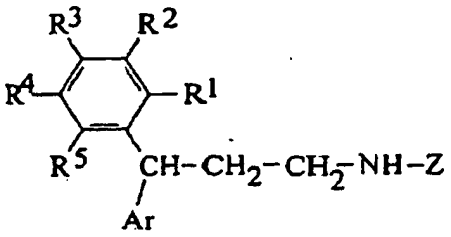
b) la réduction d'un composé de Formule III



Formule III

dans laquelle R^1 à R^7 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, ou

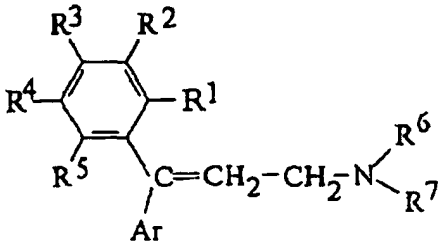
c) la N-alkylation d'une amine secondaire de Formule IV



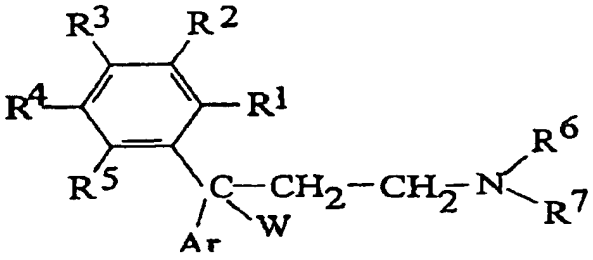
Formule IV

dans laquelle R^1 à R^5 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, et dans laquelle Z a la même signification que R^6 et R^7, ou

d) la réduction d'un composé de Formule Va ou Vb



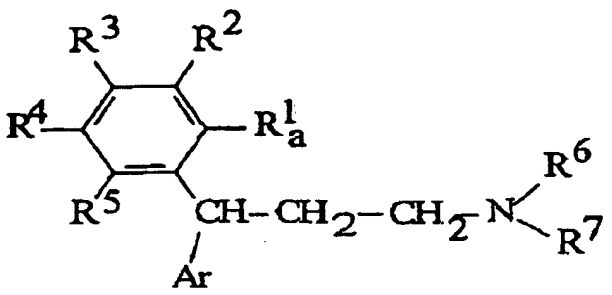
Formule Va



Formule Vb

dans laquelle R^1 à R^7 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, et dans laquelle W désigne un groupe hydroxy ou halogène, ou

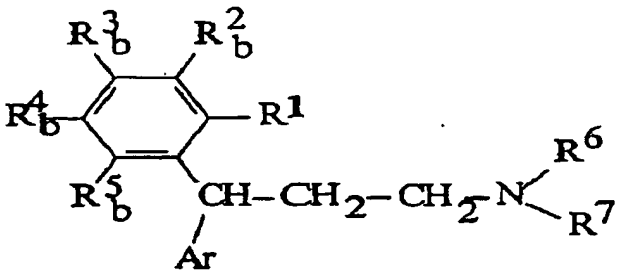
e) dans un composé de Formule VI



Formule VI

dans laquelle R^2 à R^7 et Ar sont tels que définis dans la revendication 1, et R^1a est carboxyl ou alkoxy, la conversion de R^1a en hydroxy, ou

f) dans un composé de Formule VII

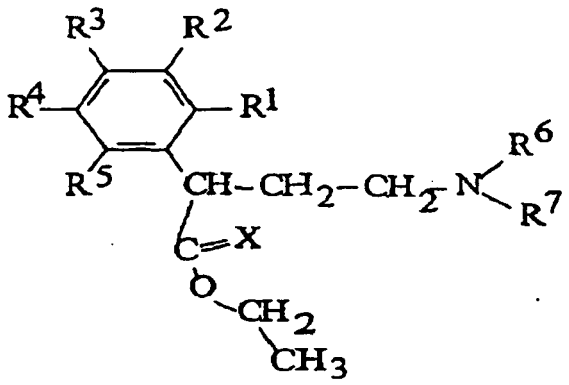


Formule VII

dans laquelle R^1, R^6, R^7 et Ar sont tels que définis dans la revendication 1, et un des éléments R^2b à R^5b est alkylène et les autres sont tels que définis dans la revendication 1 pour R^2 à R^5, la réduction de l'alkylène en alkyle, hydroxyalkyle ou dihydroxyalkyle, ou

g) dans un composé de Formule I tel que défini dans la revendication 1, la conversion d'un ou plusieurs des groupes R^1 à R^5 en un autre groupe ou en d'autres groupes R^1 à R^5, ou

h) la réaction d'un composé de Formule VIII

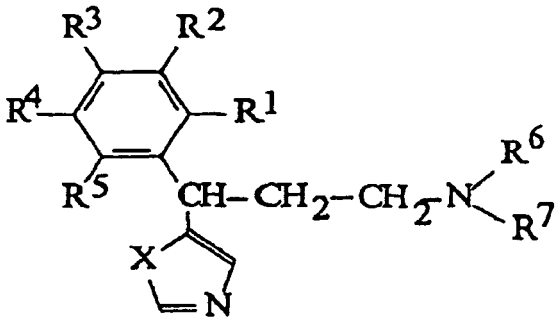


Formule VIII

dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, et X est oxygène ou soufre, avec un composé de Formule IX

$CH_3N{=}C$: formule IX

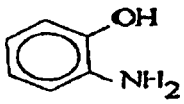
pour former un composé de Formule Ia



Formule Ia

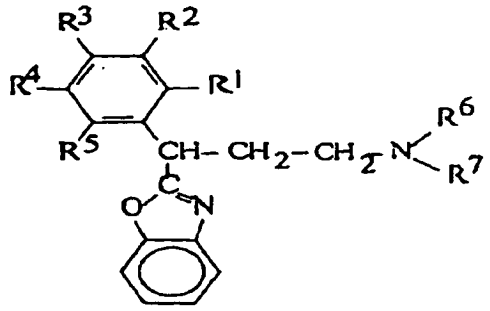
dans laquelle R^1 à R^7 et X sont tels que définis ci-dessus, ou

i) la réaction d'un composé de Formule VIII défini ci-dessus, dans lequel X est oxygène, avec un composé de Formule X



Formule X

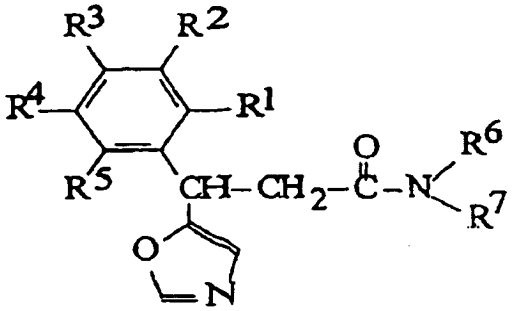
pour former un composé de Formule Ib



Formule Ib

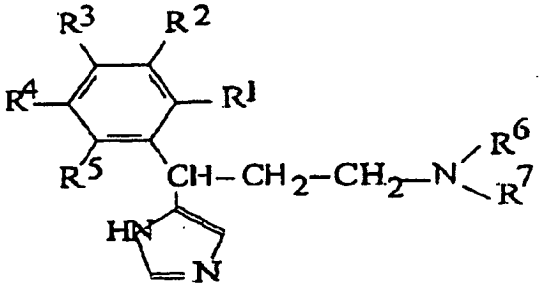
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, ou

j) la conversion d'un composé de Formule XI



Formule XI

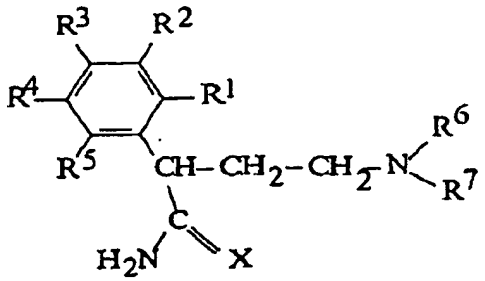
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, en un composé de Formule XII



Formule XII

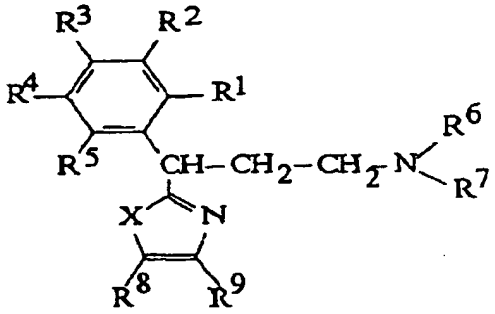
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, ou

k) la conversion d'un composé de Formule XIII



Formule XIII

dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, et X est oxygène ou soufre, en un composé de Formule XIV



Formule XIV

dans laquelle R^1 à R^7 et X sont tels que définis ci-dessus, et R^8 et R^9 sont indépendamment hydrogène ou alkyl, et

(i) si nécessaire, la séparation des groupes de protection des éléments hydroxy dans les composés obtenus,
(ii) si désiré, la conversion des bases de Formule I obtenues en leurs sels avec des acides physiologiquement acceptables, ou vice versa, et/ou
(iii) si désiré, la séparation d'un mélange obtenu d'isomères optiques en énantiomères individuels.

1,025,041

PATENT SPECIFICATION

NO DRAWINGS

1,025,041

Inventor: JOSEF KLOSA

Date of Application and filing Complete Specification: Feb. 21, 1964.
No. 7418/64.

Complete Specification Published: April 6, 1966.

Index at acceptance:—C2 C(1G5B, 1G6B1, 1G6B3, 1H1A3, 1H1C2, 2A2, 2A5, 2A7, 2A13, 2A14, 2B3A2, 2B3B, 2B3F, 2B3G1, 2B3G8, 2B3G9, 2R17, 3A13C3C, 3A13C10H, B4A2, B4A4, B4D, B4M); A5 B2S

Int. Cl.:—C 07 c, d // A 61 k

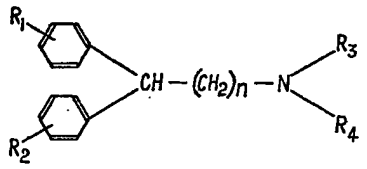
COMPLETE SPECIFICATION

Process for the manufacture of Diphenylalkylamines

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

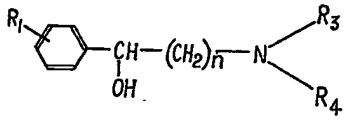
The present invention relates to a process for the manufacture of diphenylalkylamines which have a beneficial physiological effect, especially on the heart and on blood circulation. The invention also relates to processes for the manufacture of pharmaceutical preparations, having cardiac and circulatory action containing diphenylalkylamines or their physiologically tolerable salts as the active ingredients.

The present invention provides diphenylalkylamines of the formula



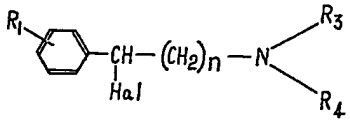
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, especially chlorine, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups each having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n is 1 or 2, by reacting a 1-phenyl-1-hydroxy-alkylamine of the formula



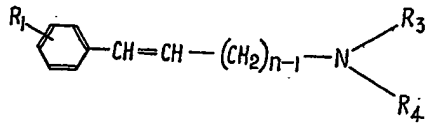
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



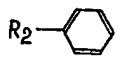
(III)

in which Hal represents a halogen atom, preferably a chlorine atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meanings given above, with an aryl compound of the formula



(V)

in which R_2 has the meaning given above, in

[Pric

the presence of Friedel-Crafts catalysts such for example as gallium trichloride, boron trifluoride or, preferably, aluminium trichloride.

The following phenylalkyl compounds may be used as one reactant in the process of the present invention:

1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - *p* - methoxy - phenyl - 1 - hydroxy - 3-(1 - phenyl - propyl - (2) - amino) - propane,
1 - *m* - chlorophenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - amino) - propane,
1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - *m* - methoxy - phenyl - propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (2 - phenyl-ethylamino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1- phenyl-propyl - (2) - methylamino) - propane,
1 - phenyl - 1 - hydroxy - propylamine - (3),
1 - phenyl - 1 - hydroxy - ethylamine - (2),
1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane,
1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, and the analogous
1 - phenyl - 1 - chloro - compounds and
1 - phenyl - 1,2 - unsaturated compounds.

As the second reactant in the process of the present invention, there may be mentioned, for example, benzene, toluene, chlorobenzene, methoxybenzene, ethoxybenzene and isopropylbenzene.

The reaction is carried out in a suitable solvent. As solvent there may be used, the second reactant in the process, which is then to be used in excess, or as an inert solvent, nitrobenzene or chlorinated hydrocarbons such as for example as carbon tetrachloride or tetrachloroethane.

The reaction is carried out at a temperature in the range of 50 and 200°C, preferably in the range of 60 and 140°C. In practice, the reaction is carried out at the boiling temperature of the solution used.

In an advantageous method for carrying out the process of the present invention, the selected 1-phenyl-1-hydroxy-alkylamine is converted with a Lewis acid, for example, aluminium chloride, in a suitable solvent, for example, benzene, and with the aid of an appropriate halogenating agent, preferably an acid chloride of sulphur, for example, thionyl chloride, into the corresponding chloride; the hydrochlorides of the 1-phenyl-1-chloro-compounds thus obtained are generally well crystallizable. The 1-phenyl-1-chloroalkyl-amines thus obtained are condensed at elevated temperature in one of the mentioned solvents containing the desired reactant and the Friedel-Crafts catalyst to yield the diphenyl-alkyl-amines. These two process steps may be carried out in one vessel.

According to another advantageous method of operation, the 1-phenyl-1-hydroxy-alkyl-amines can be reacted directly with the second reactant in the solvents mentioned above. The reaction may be carried out in the same way starting from the mentioned 1-phenyl-1,2-unsaturated alkylamine compounds.

As basic compounds, the products of the present invention may be converted into the corresponding salts by reacting them with inorganic or organic acids, preferably physiologically tolerable inorganic or organic acids. As inorganic acids, there may be used for example, hydrohalic acids, for example hydrochloric acid, sulphuric acid, phosphoric acid or amido-sulphonic acid. As organic acids, there may be used, for example, acetic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, maleic acid, succinic acid, tartaric acid, salicyclic acid, or citric acid.

The products of the present invention may be administered parenterally or orally, as such or in the form of their salts, if desired or required in admixture with pharmaceutically usual carriers, if desired, in unit dosage form. In the case of oral application, they may be used preferably as tablets or dragees into which they, as the active substances, have been made up with the usual carriers such as lactose, starch, tragacanth and magnesium stearate.

The processes hitherto known and used for the preparation of the products of the invention are difficult and time-consuming. Some of the starting materials required for these processes are difficulty accessible. The present process makes the products more readily available as it may be carried out on the scale required for industrial use.

The following Examples illustrate the invention.

EXAMPLE 1

15.1 g of 1-phenyl-1-hydroxy-propylamine-(3) were boiled for 30 minutes with 14.5 g of phenylacetone in 50 cc of benzene and the water formed was removed by distillation with benzene. The oily residue was then taken up in 30 cc of methanol and 5 cc of water. 1.5 g of sodium boron hydride was introduced portionwise into this solution, during which time the temperature of the reaction mixture rose to 40—50°C. The reaction mixture was then heated for 30 minutes on the water bath and the solvent was removed by distillation. The oily residue was extracted with ether and alcoholic hydrochloric acid was added to the ether extract until the mixture was turbid. 25 g of 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride crystallized; the compound was found to melt at 144—146°C.

25 g of the compound thus obtained were introduced portionwise, at room temperature, into a solution of 40 cc of thionyl chloride in 80 cc of benzene. A strong evolution of hydrogen chloride and sulphur dioxide set in. After some time, the hydrochloride of 1-phenyl-1-chloro - 3 - (1 - phenyl - propyl - (2) - amino) - propane crystallized. Separation was completed by the addition of ether. 24 g of the compound which showed a melting point of 138—144°C were obtained. 10 g of this hydrochloride were suspended in 40 cc of benzene and 8 g of anhydrous aluminium chloride were added, the temperature being at about 50°C. The whole was then heated for 30 minutes under reflux. After cooling, the reaction mixture was poured in a mixture of 20 cc of concentrated hydrochloric acid, 10 cc of water and 100 g of ice. After several hours standing and after addition of ether, the hydrochloride of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane crystallized in almost colourless crystals. The crude yield was 11.2 g; the compound was found to melt at 186—188°C (from aqueous methanol 190—192°C).

EXAMPLE 2

15 g of 1-phenyl-1-hydroxy-propylamine-(3) were introduced portionwise into a mixture of 16 cc of thionyl chloride and 30 cc of benzene. The whole was heated for 20 minutes under reflux on the water bath. After several hours standing, crystallization was completed by the addition of ether. 18.5 g of 1 - phenyl - 1 - chloro - propylamine - (3)-hydrochloride having a melting point of 110—112°C were obtained. 10 g of the hydrochloride thus obtained were suspended in 40 cc of benzene and 12 g of anhydrous aluminium chloride were added portionwise. After heating for 30 minutes on the water-bath, the reaction mixture was poured in a mixture of hydrochloric acid, water and ice. The hydrochloride of 1,1-diphenyl-propyl-amine-(3) melting at 206—209°C crystallized out. The yield was 12 g. After recrystallization from water, the product was found to melt at 217—218°C.

EXAMPLE 3

10 g of 1-phenyl-1-hydroxy-2-morpholino-ethane were dissolved in 30 cc of benzene. 15 g of anhydrous aluminium chloride were added portionwise in such a manner that the reaction mixture did not boil. The reaction mixture was then heated for 30 minutes on a water bath. After cooling, it was poured in a mixture of ice, water and concentrated hydrochloric acid. After some minutes, 1,1-diphenyl - 2 - morpholino - ethane - hydrochloride crystallized out. The yield was 14.6 g. After recrystallization from a mixture of isopropanol and ether, the compound was found to melt at 211—213°C.

EXAMPLE 4

8 g of anhydrous aluminium chloride were introduced in a solution of 5 g of 1-phenyl-1-hydroxy-2-benzylamino-ethane in 20 cc of toluene in such a manner that the toluene did not boil. The reaction mixture was then heated for 30 minutes to boiling temperature and after cooling it was poured into a mixture of ice, water and concentrated hydrochloric acid. 1-phenyl-1-*p*-tolyl-2-benzylamino-ethane-hydrochloride crystallized in a yield of 92%. By recrystallization from a mixture of isopropanol and ether, there were obtained colourless needles melting at 203—205°C.

EXAMPLE 5

12 g of styrene oxide were mixed with 13.5 g of 1-phenyl-propylamine-(2) and heated for several hours to 100—120°C. 1 - phenyl - 1 - hydroxy - 2 - (1 - phenyl-propyl - (2) - amino) - ethane was obtained in the form of an almost colourless oil. 20 g of anhydrous aluminium chloride were added portionwise to a solution of this oil in 80 cc of benzene. The mixture was heated for 30 minutes under reflux to the boiling temperature on the water bath and, after cooling, it was poured into a mixture of ice, water and hydrochloric acid. The hydrochloride of 1,1-diphenyl - 2 - (1 - phenyl - propyl - (2)-amino) - ethane separated in the form of an oil. The free base was isolated by addition of soda lye and extraction with ether. After addition of an alcoholic solution of maleic acid, the maleate, which was found to melt at 168—170°C, crystallized in a yield of 88%.

EXAMPLE 6

4 cc of water were added to a solution of 14 g of 1-phenyl-1-hydroxy-2-amino-ethane and 13.7 g of phenylacetone in 40 cc of methanol and subsequently 1.5 g of sodium boron hydride were added portionwise. After a one hour standing at room temperature, the reaction mixture was concentrated by evaporation under reduced pressure. The oily residue was taken up in 40 cc of toluene, 20 g of anhydrous aluminium chloride were added portionwise and the mixture was further treated as described in Example 5. 1 - phenyl - 1 - *p* - tolyl - 2 - (1 - phenyl-propyl - (2) - amino) - ethane in the form of a colourless oil was obtained. After addition of maleic acid, the maleate which was found to melt at 166—168°C. was obtained.

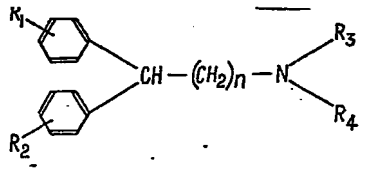
EXAMPLE 7

30 g of anhydrous aluminium chloride were added portionwise to a suspension of 29 g of 1 - phenyl - 2 - cinnamylamino - propane-hydrochloride melting at 237—240°C (prepared by condensation of cinnamic aldehyde with 1-phenyl-propyl-amine-(2) and reduction of the Schiff-base thus obtained with sodium boron hydride) in 100 cc of benzene and the reaction mixture was subsequently heated for 45 minutes to the boiling temperature. After the reaction mixture had cooled, it was

poured in a mixture of ice and hydrochloric acid as described in Example 1. After addition of ether, the crystals were separated by filtration, dissolved in methanol in order to separate mineral salts and then the compound was precipitated by the addition of water. 26.5 g of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride were obtained; the compound was found to melt at 190—192°C after recrystallization from isopropanol.

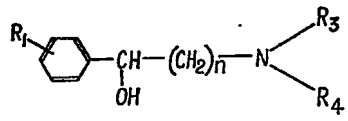
WHAT WE CLAIM IS:—

1. A process for the manufacture of diphenylalkylamines of the formula



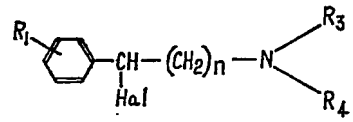
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n represents 1 or 2, wherein a 1-phenyl-1-hydroxy-alkylamine of the formula



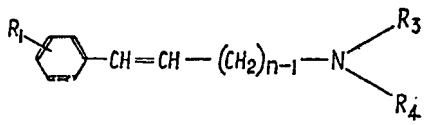
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



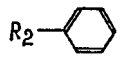
(III)

in which Hal represents a halogen atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meaning given above, is reacted with an aryl compound of the formula

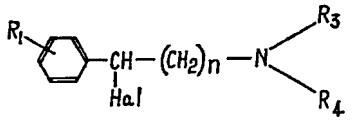


(V)

in which R_2 has the meaning given above, in the presence of Friedel-Crafts catalysts.

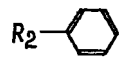
2. A process as claimed in claim 1, in which R_1 or R_2 represents or both R_1 and R_2 represent chlorine.

3. A process as claimed in claim 1 or claim 2, in which a 1-phenyl-1-chloroalkylamine of the formula



(III)

in which R_1, R_3, R_4, and n have the meanings given in claim 1 and Hal represents chlorine is reacted with an aryl compound of the formula



(V)

in which R has the meaning given in claim 1, in the presence of Friedel-Crafts catalysts.

4. A process as claimed in any one of claims 1 to 3, wherein the Friedel-Crafts catalyst is aluminium trichloride.

5. A process as claimed in any one of claims 1 to 4, wherein the Friedel-Crafts catalyst is gallium trichloride or boron trifluoride.

6. A process as claimed in claim 1, wherein 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane is used as a reactant.

7. A process as claimed in claim 1, wherein 1 - *p* - methoxy - phenyl - 1 - hydroxy-3 - (1 - phenyl - propyl - (2) - amino) - propane is used as a reactant.

8. A process as claimed in claim 1, wherein 1 - *m* - chloro - phenyl - 1 - hydroxy - 3 - (1-

phenyl - propyl - (2) - amino) - propane is used as a reactant.

9. A process as claimed in claim 1, wherein 1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane is used as a reactant.

10. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - *m*-methoxy - phenyl - propyl - (2) - amino)-propane is used as a reactant.

11. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane is used as a reactant.

12. A process as claimed in claim 1, wherein 1 - phenyl - 1- hydroxy - 3 - (2 - phenyl-ethylamino) - propane is used as a reactant.

13. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - methylamino) - propane is used as a reactant.

14. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - propylamine-(3), is used as a reactant.

15. process as claimed in claim 1, wherein 1 - phenyl - hydroxy - ethylamine-(2), is used as a reactant.

16. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane, is used as a reactant.

17. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, is used as a reactant.

18. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxy alkylamine there is used the corresponding 1-phenyl-1-chloroalkylamine.

19. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxyalkylamine there is used the corresponding 1-phenyl-alken-1,2-ylamine.

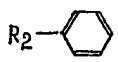
20. A process as claimed in any one of claims 1 to 19, wherein benzene, toluene, chlorobenzene, methoxybenzene, ethoxy-benzene, or isopropylbenzene is used as second reactant.

21. A process as claimed in any one of claims 1 to 20, carried out at a temperature within the range of 50 to 200°C.

22. A process as claimed in claim 21, carried out at a temperature within the range of 60 to 140°C.

23. A process as claimed in any one of claims 1 to 22, carried out in an inert solvent.

24. A process as claimed in any one of claims 1 to 23, wherein an excess of the reaction component of the formula



where R_2 has the meaning given in claim 1, is used as a solvent.

25. A process as claimed in claim 23 or claim 24, carried out at the boiling temperature of the solution used.

26. A process as claimed in claim 1 carried out substantially as described in any one of the Examples herein.

27. Diphenylalkylamines whenever prepared by the process claimed in any one of claims 1 to 26.

28. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

29. 1,1 - diphenyl - propylamine - (3) whenever prepared by a process as claimed in claim 1.

30. 1,1 - diphenyl - 2 - morpholino ethane whenever prepared by a process as claimed in claim 1.

31. 1 - phenyl - 1 - *p* - tolyl - 2 - benzyl-aminoethane whenever prepared by a process as claimed in claim 1.

32. 1,1 - diphenyl - 2 - (1 - phenyl-propyl - (2) - amino)ethane whenever prepared by a process as claimed in claim 1.

33. 1 - phenyl - 1 - *p* - tolyl - 2 - (1-phenyl - propyl - (2) - amino - ethane whenever prepared by a process as claimed in claim 1.

34. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

35. A salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenylalkylamine having been prepared by a process as claimed in claim 1.

36. A physiologically tolerable salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenylalkylamine having been prepared by a process as claimed in claim 1.

37. Pharmaceutical preparations containing a diphenylalkylamine as claimed in any one of claims 27 to 34 in admixture or conjunction with a pharmaceutically acceptable excipient.

38. Pharmaceutical preparations containing a physiologically tolerable salt of a diphenylalkylamine as claimed in claim 36, in admixture or conjunction with a pharmaceutically acceptable excipient.

39. Pharmaceutical preparations as claimed in claim 37 or claim 38 in unit dosage form.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 077 912 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
03.07.2002 Bulletin 2002/27

(21) Application number: **99924929.5**

(22) Date of filing: **11.05.1999**

(51) Int Cl.[7]: **C07C 1/00**, C07C 217/62, C07C 217/48, C07C 219/28, C07C 219/22, C07D 207/06, C07D 295/06, C07C 271/08, C07F 7/18, C07C 307/02, A61K 31/135, A61K 31/325, A61K 31/40, A61K 31/435

(86) International application number:
PCT/EP99/03212

(87) International publication number:
WO 99/58478 (18.11.1999 Gazette 1999/46)

(54) **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**

3,3-DIPHENYLPROPYLAMINDERIVATE

NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **12.05.1998 EP 98108608**

(43) Date of publication of application:
28.02.2001 Bulletin 2001/09

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- **LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application**

Printed by Jouve, 75001 PARIS (FR)

EP 1 077 912 B1

Description

[0001] The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

[0002] In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

[0003] Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

[0004] Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

[0005] A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

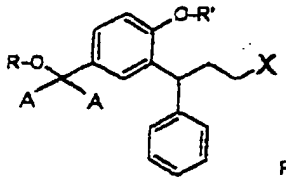
[0006] WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0007] However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

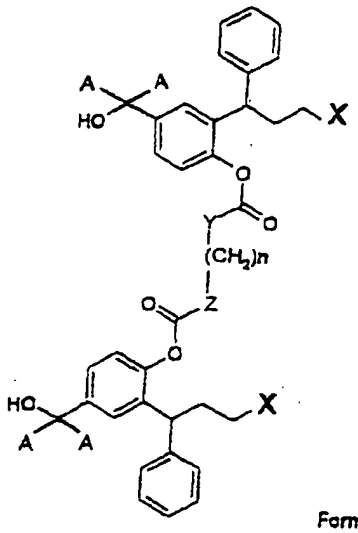
[0008] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

[0009] A further object of the invention is to provide novel prodrugs of antimuscarinic agencs with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

[0010] According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII'



Formula I



Formula VII'

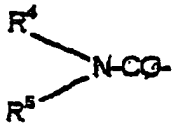
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

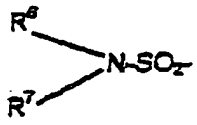
c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)



wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)

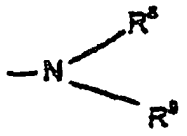


wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,
X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,
A represents hydrogen (^1H) or deuterium (^2H),
n is 0 to 12
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

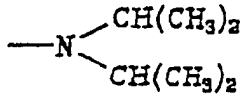
[0011] The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride and hydrobromide.

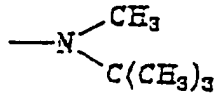
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

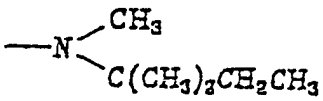
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

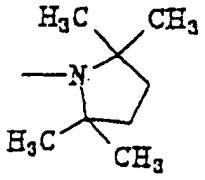
[0014] According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

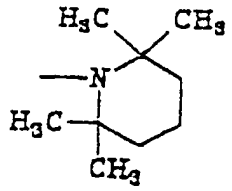
[0015] Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

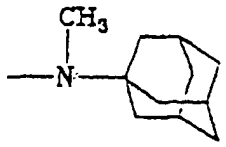
a) 

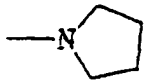
b) 

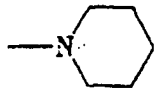
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

[0016] The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds .

[0017] In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

[0018] The term "substituted or unsubstituted benzyl" denotes a benyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen and nitro. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

[0019] In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

[0020] The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-) and anthryl- ($C_{14}H_9$-). Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

[0021] The term "benzoyl" denotes an acyl group of the formula $-CO-C_6H_5$ wherein the phenyl ring may have one or more substituents.

[0022] Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

[0023] The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)-wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

[0024] The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

[0025] The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

[0026] The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and corresponding carbohydrate groups are, for example, described in Aspinal. The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

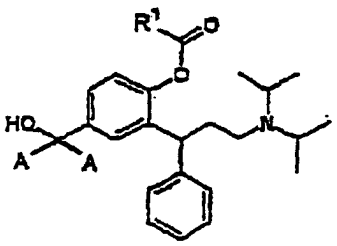
[0027] The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates and imidazolides.

[0028] The term "Bn" as used herein denotes a benzyl group.

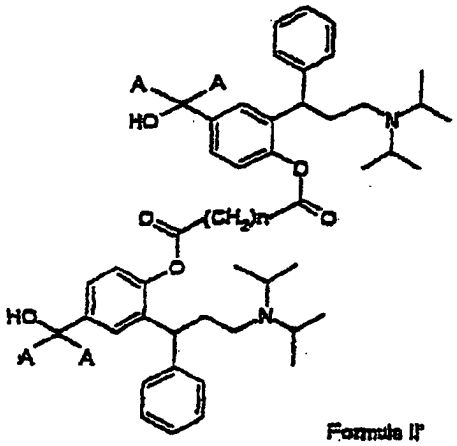
[0029] Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

[0030] Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



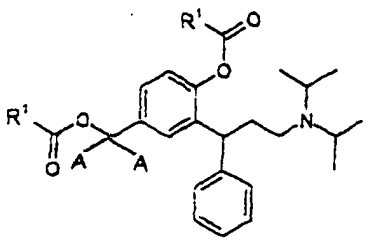
Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclopentanecarboxylic acid 2-(3-diisoprcpylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis- [2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



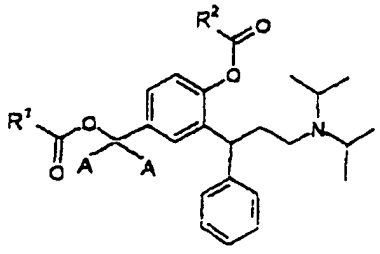
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



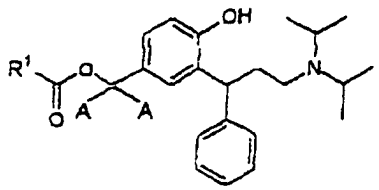
Formula IV

wherein R^1 is as defined above
and
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl
with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



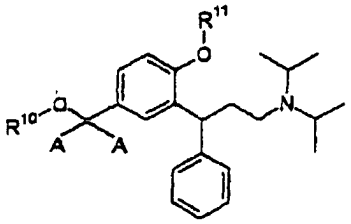
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3- (3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

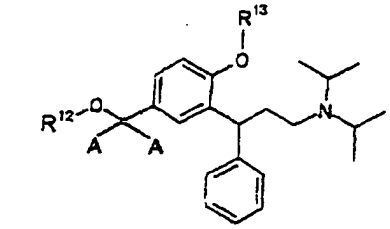
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

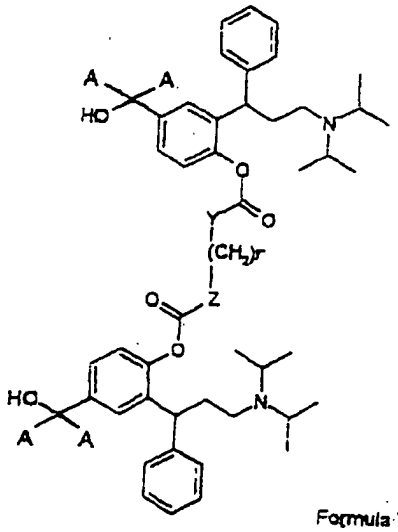
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(+) -2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±) -2- (3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert. -butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

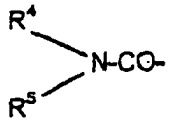


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

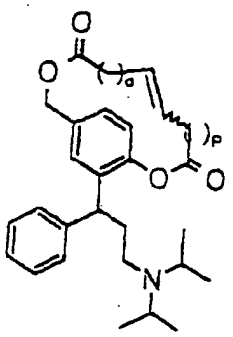
Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4- [2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic ac-

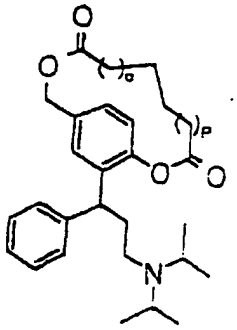
id 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



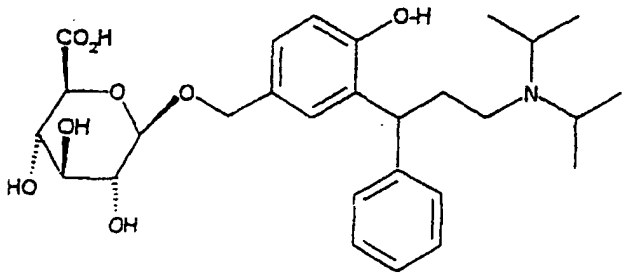
Formula IX'

wherein o and p are the same or different and represent the number of methylene units { CH_2 } and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylaminophenylpropyl)-4-hydroxymethyl-phenol

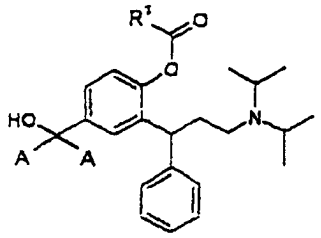
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

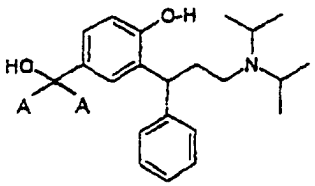
[0031] The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

[0032] A process for the production of phenolic monoesters represented by the general formula II

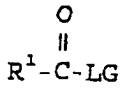


Formula II

as defined above, which comprises treatment of a compound of the formula

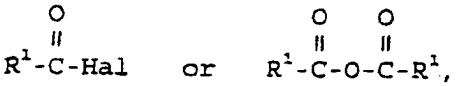


with an equivalent of an acylating agent selected from



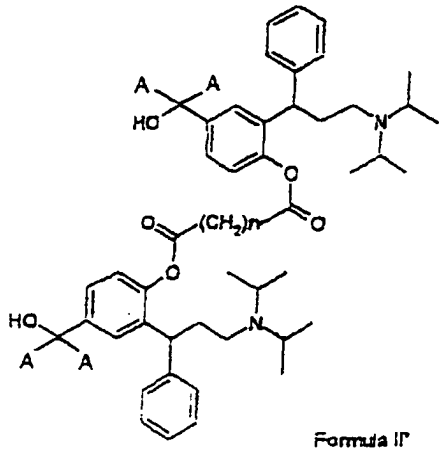
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

[0033] Preferably, the acylating agent is selected from



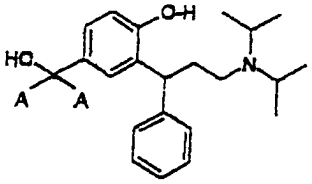
wherein Hal represents a halogen atom, preferably a chlorine. atom, and R^1 is as defined above.

[0034] A process for the production of phenolic monoesters represented by the general formula II'

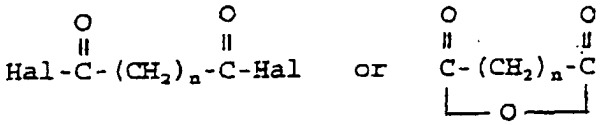


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

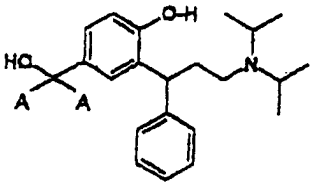


with an acylating agent selected from



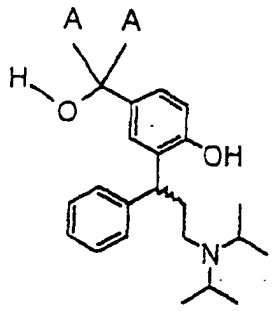
wherein Hal represents a halogen atom, preferably a chlorine atom.

[0035] Hence, in these processes, an Intermediate B having the formula

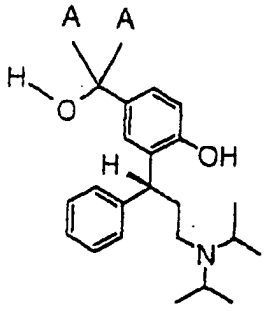


is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

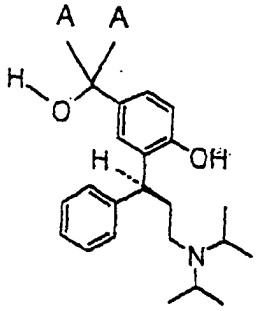
[0036] The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



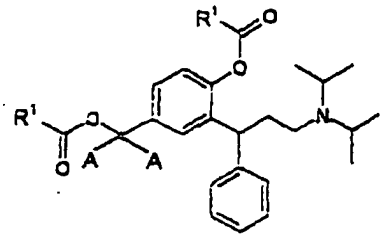
Intermediate R-(+)



Intermediate S-(-)

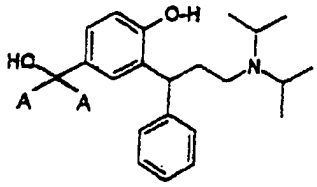
[0037] Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991).

[0038] The identical diesters represented by the general formula III



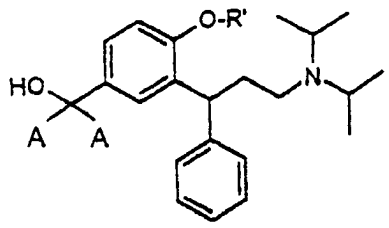
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



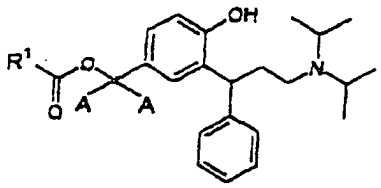
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

[0039] Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



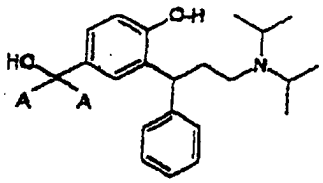
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

[0040] Benzylic monoesters represented by the general formula V



Formula V

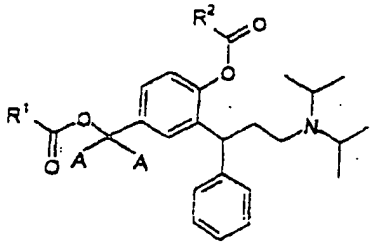
wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula



at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

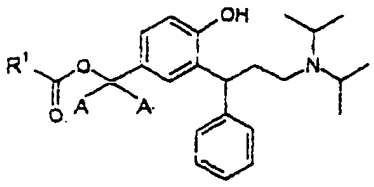
[0041] Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

[0042] The mixed diesters represented by the general formula IV



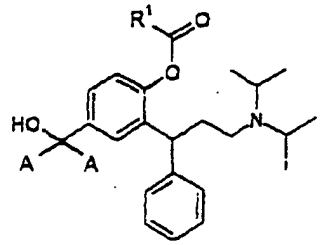
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

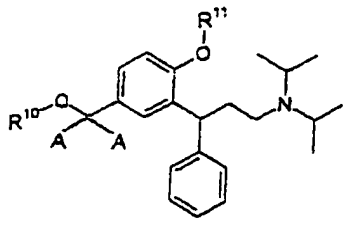


Formula II

as defined hereinbefore.

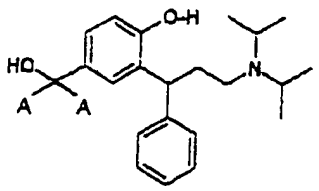
[0043] In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

[0044] Ethers represented by the general formula VI



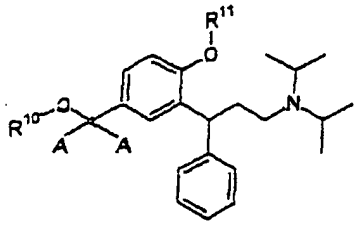
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



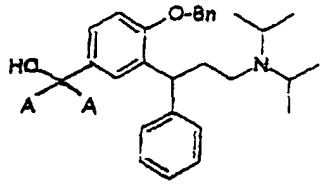
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

[0045] A further process for the preparation of ethers represented by the general formula VI

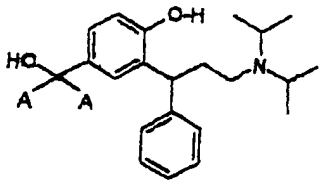


Formula VI

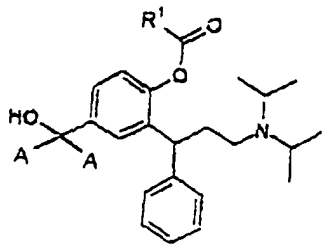
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

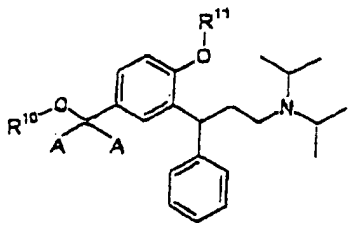


and



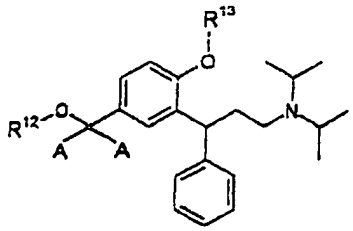
Formula II

or



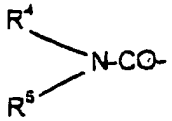
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or

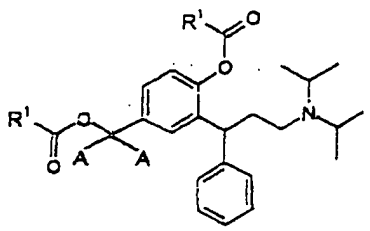


Formula VII

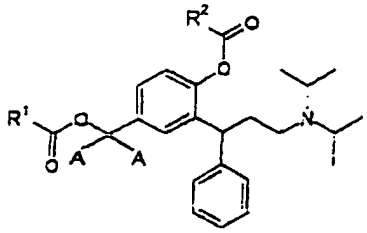
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



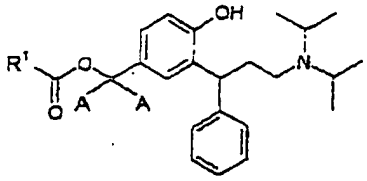
wherein R^4 and R^5 are as defined above
or of benzylic acylates selected from



Formula III



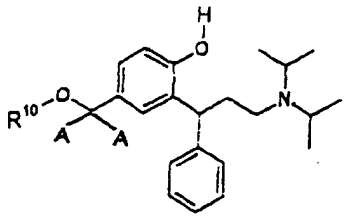
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

[0046] Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

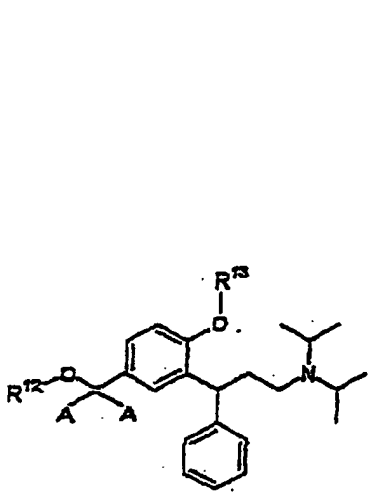


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

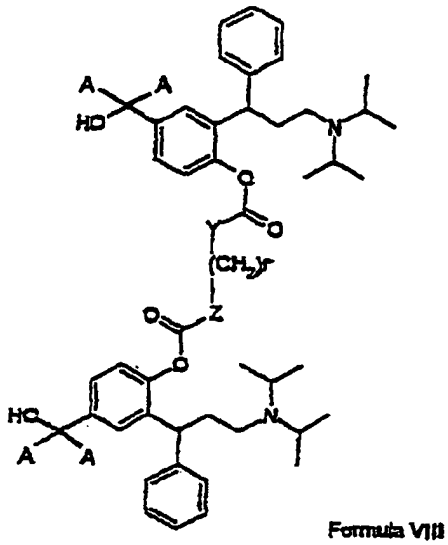
[0047] In summary, regioselective modification of the *benzylic hydroxy groups is* achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

[0048] Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

[0049] Carbonates and carbamates represented by the general formulae VII and VIII

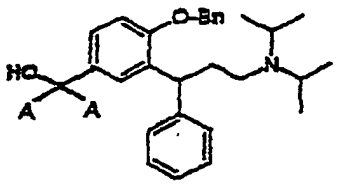


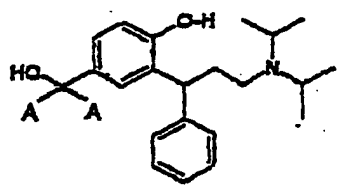
Formula VII

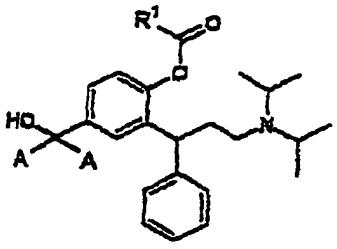


Formula VIII

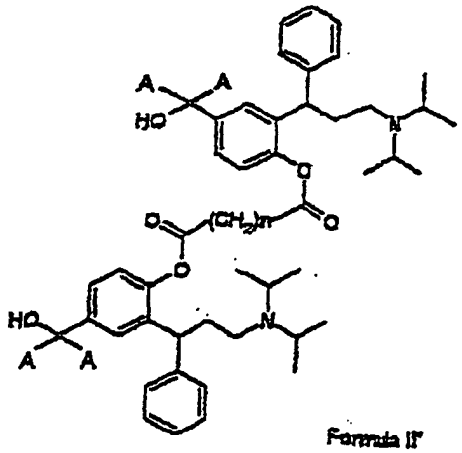
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



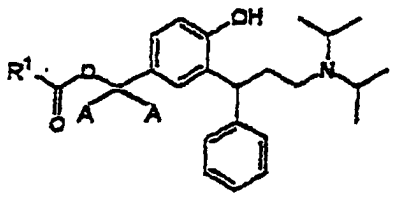




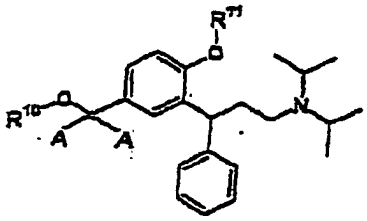
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined above with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

[0050] The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents -C(=O)-Y-R^3, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

[0051] The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

[0052] They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

[0053] The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection or for nasal spray administration, in accordance with accepted pharmceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum and colloidal silicon dioxide. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents and buffers.

[0054] The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups and elixirs in the form of sterile solutions, suspensions or emulsions for parenteral administration.

[0055] The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

[0056] The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

[0057] The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

[0058] All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^1H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

[0059] Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.

Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%) ; (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%) ; (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).

Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.

Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.

IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.

Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives. Combined liquid chromatography-mass spectrometry (LC-MS) :

Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

[0060] An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR ($CDCl_3$) : 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

[0061] A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with echylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one,* m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$) : 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

[0062] A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$) : 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0063] A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid methyl ester* (0,391 g, 0,92 mmol)

in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid,* colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$) : 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, M^+), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr) : 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

[0064] Alternatively, the crude reaction mixture from the above described synthesis of *(±) -3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0065] Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid* (815.6 g, 1.85 mol) and 1S, 2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2- benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$) : 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

[0066] 1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

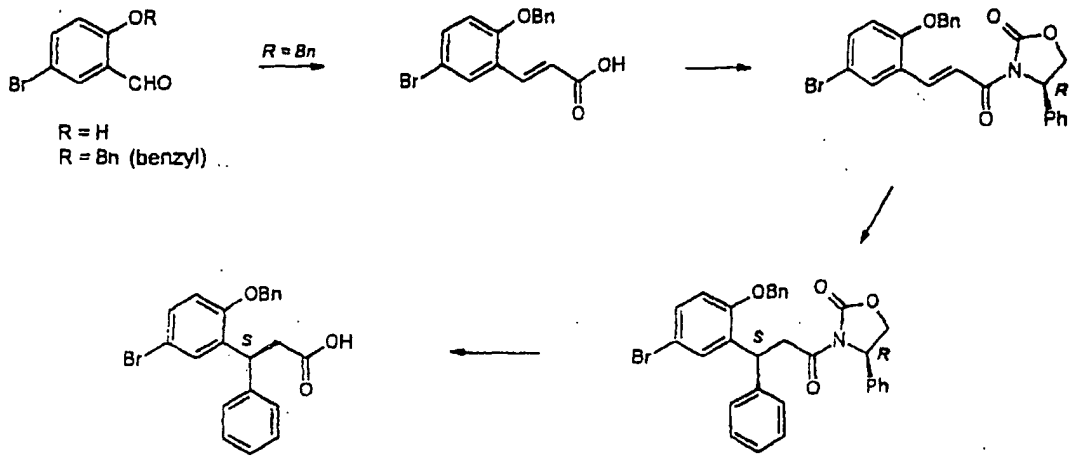
S-(+)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionic acid

[0067] The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was re-dissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$) : 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

[0068] *S- (+)-3- (2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0069]



2-Benzyloxy-5-bromobenzaldehyde

[0070] To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromobenzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

[0071] A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one

[0072] Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3- [3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

[0073] To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3- [3- (2-Benzyloxy-5-bromophenyl)-acryloyl] -(4R)-4-phenyloxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0074] A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl) - (3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

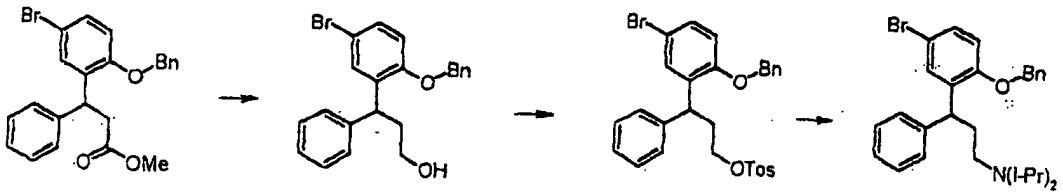
[0075] HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

[0076] **R-(-)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionic acid** Conjugate organocuprate addition of phenylmagnesiumbromide to-*3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzylcxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystallizations, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route

[0077]



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

[0078] A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, (±)-3-*(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol.* NMR ($CDCl_3$) : 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

[0079] The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

[0080] A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$) : 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16,

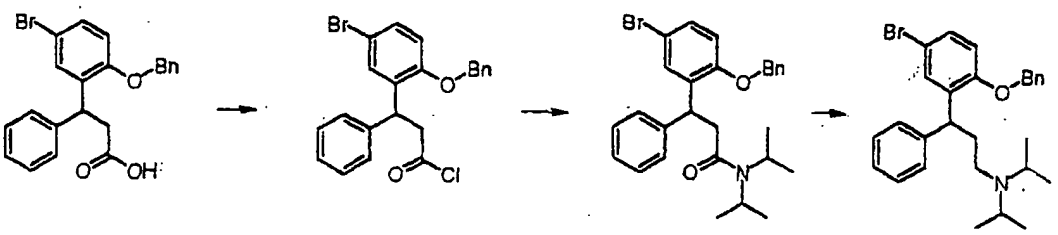
155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0081] A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9% yield), tlc: (2) 0.49. NMR ($CDCl_3$) : 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route

[0082]



S-(+)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionyl chloride

[0083] Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 9). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

[0084] A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temperature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$) : 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3- (2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

[0085] The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0086] To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tecrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent

was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%). of the title compound as a viscous colourless oil, tlc: (4) 0.86. The NMR spectrum corresponds to the product, obtained from the tosylate precursor (see above).

S-(+)-[3- (2-Benzyloxy-5-bromophenyl)-3-phenylpropyl] -diisopropylamine

[0087] Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0088] Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

[0089] The optical purities were determined by chiral HPLC using Chiralpak OD columns.

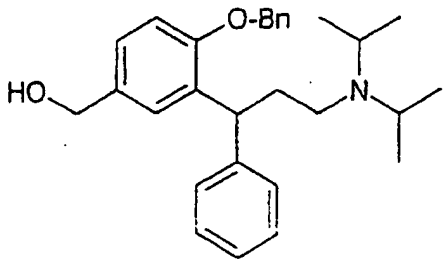
(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

[0090] An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD) : 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±) - [4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

[0091] The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$) : 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl] - [C^2H]methanol

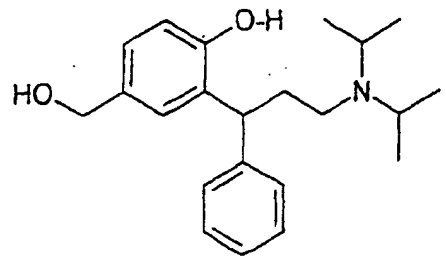
Intermediate d_2-A (n = 2)

[0092] Repetition of the above described reduction of the methylester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$) : 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03,128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Intermediate B (n = 1)

[0093] A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$) : 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.
Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0094] *Hydrogenolysis of S-(-)-[4-benzyloxy-3- (3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S- (+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$) : 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.
S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6) : 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0095] Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).
R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water) ; NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.
S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

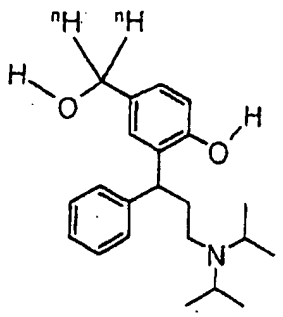
Intermediate d_2-B (n = 2)

[0096] A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl] - [$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$) : 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137,17, 144.30. 155.52.

[0097] A solution of the above (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc : (4) 0.57 (starting material 0.77). NMR ($CDCl_3$) : 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



Intermediate d_2-B

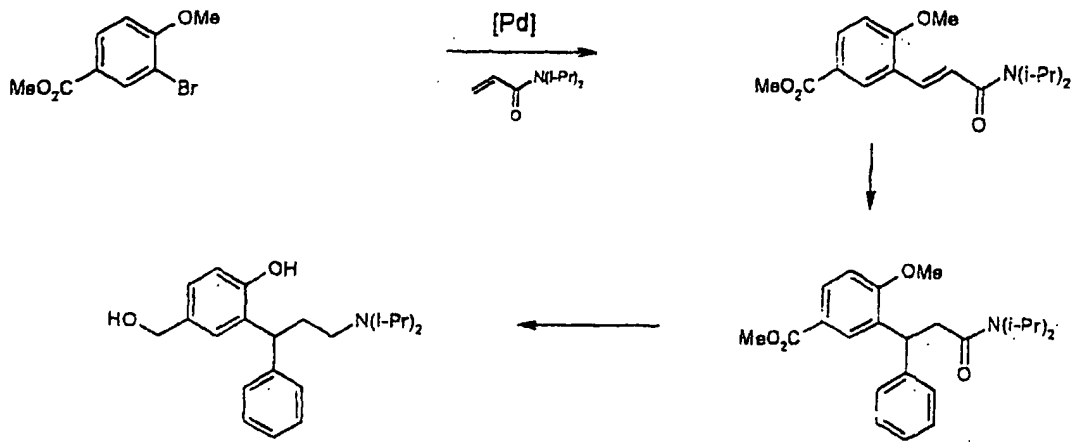
n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$] methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B

[0098]



Intermediate B

N,N-Diisopropyl-acrylamide

[0099] A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$) : 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

[0100] The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.
A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tic (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40. NMR (CD_2Cl_2) : 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07. MS (EI, DI, 105°C) : 319 (M^+, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxybenzoic acid methyl ester)

[0101] The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.
A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclohexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave
(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide
as a viscous slightly yellow syrup (1.8 g, 44% yield). NMR (CD_2Cl_2) : 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C) : 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0102] A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room temperature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0103] A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of
S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate
in 33% yield, tlc: (4) : 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD) : 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.
[0104] A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol)
[0105] Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+) - (2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids

[0106] A stirred solution of (±)-*2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5,00 mmol carboxylic acid monochloride for compounds of formula II, 2.50 mmol for compounds of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

[0107] To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

[0108] A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

[0109] The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4 hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$) : 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$) : 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4) ; NMR ($CDCl_3$) : 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%) ; GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%) ; GC-MS/P-CI (ammonia, trimethylsilyl derivative) : 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4) ; NMR ($CDCl_3$) : 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$) : 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$) : 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1) ; NMR ($CDCl_3$) : 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD) : 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$) : 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$) : 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%) ;gradually crystallized upon refrigeration; NMR ($CDCl_3$) : 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70. 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 154.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl-)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4) ; colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform) ;
NMR ($CDCl_3$) : 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81; 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24 ; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$) : 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$) : 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc : (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$) : 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%),

223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$) : 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 (M^+, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$) : 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 (M^+, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$) : 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 (M^+ 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$) : 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 (M^+, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$) : 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$) : 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$) : 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 (M^+, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD) : 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$) : 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$) : 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$) : 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

[0110] *(±)*-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triechylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

[0111] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta 37:* 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia) : 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative) : 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$) - 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc : R_f 0.82 (4) ; NMR ($CDCl_3$) : 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid *4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester*, tlc: R_f 0.86 (4); NMR ($CDCl_3$) : 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; GC-MS/P-CI (ammonia) : 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$) : 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4) ; NMR ($CDCl_3$) : 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4) ; NMR ($CDCl_3$) : 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1- phenylpropyl)-phenyl ester
Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR ($DMSO-d_6$) : 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed diesters

[0112] Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters.

Working up and physical properties corresponded to the bases and salts described above.

[0113] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4 formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$) : 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4) ; NMR ($CDCl_3$) : 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$) : identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4- acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$) : 17.14, 18.53, 21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$) : 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.29, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$) : 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4) ; NMR ($CDCl_3$) : 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4) ; NMR ($CDCl_3$) : 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

[0114] A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

[0115] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4 hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$) : 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2) ; NMR ($CDCl_3$) : 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2) ; NMR ($CDCl_3$) :

19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2) ; NMR ($CDCl_3$) : 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4) ; NMR ($CDCl_3$) : 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4) ; NMR ($CDCl_3$) : 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$) : 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

[0116] A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

[0117] Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

[0118] Molar equivalents of bases of formula VI (R^{11} = H) , dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

[0119] In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl phenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m.p. 161°C; NMR (CD_3OD) : 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 12.9.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative) : 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD) : 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol, NMR ($CDCl_3$) : 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol, NMR ($CDCl_3$) : 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M\text{-}HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol, NMR ($CDCl_3$) : 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$) : 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$) : 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$) : 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$) : 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$) : 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$) : 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$) : 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$) : -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$) : -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±) - {3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine, tlc: R_f 0.94 (3) ; GC-MS/N-CI (methane) : 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$) : 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$) : 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$) : 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

[0120] A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane 20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

[0121] N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

[0122] Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.

Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

[0123] The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

[0124] In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative) : 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6) : 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$) : 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$) : 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$) : 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$) : 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72, 130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3) ; NMR ($CDCl_3$) : 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$) : 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 35.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl) -4-N,N-diethylcarbamoyloxybenzyl ester

NMR ($CDCl_3$) : 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

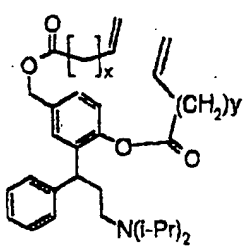
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6) ; dihydrochloride m.p. 142.5-145.6°C

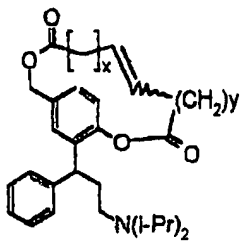
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

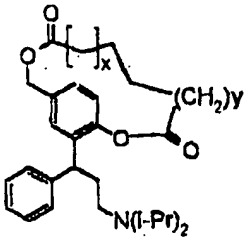
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)

[0125]







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

[0126] A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/ heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy methyl)-phenyl ester* as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$) : 18.95, 20.77, 27.75, 23.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3 -diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

[0127] Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylami-

no)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers.
NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

[0128] A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.
NMR ($CDCl_3$) : 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

[0129] All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

[0130] A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 1.5 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.
The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate 3 of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

[0131] The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

[0132] The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$) :

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm
CH resonances of the poly-lactyl chain: 5.10-5.30 ppm
CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.
Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{\mathbf{CH_2}}$), 2.40-2.80 ($N\underline{\mathbf{CH_2}}$), 3.30-3.50 ($N\underline{\mathbf{CH}}$), 4.45-4.55 ($\underline{\mathbf{CH}}CH_2$), 4.70-4.80 ($\underline{\mathbf{CH_2}}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{\mathbf{CH}}$).

h) Inorganic ester

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

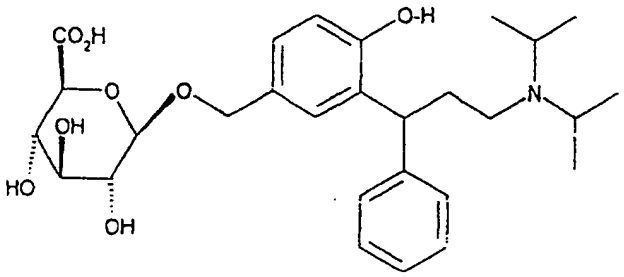
Hydrochloride

[0133] To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$) : 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl) -4-hydroxymethylphenol

((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)

[0134]



[0135] A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosylbromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester,* colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.
NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.
[0136] A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,
amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

[0137] A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

[0138] The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

[0139] In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

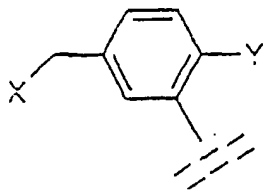
[0140] The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

[0141] The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

[0142] They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

[0143] The prodrugs introduced in the assay show the following chemical structure:



chemical structure X-/-Y		
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
ACO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

[0144] The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

[0145] The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate

to produce the corresponding carboxylic acid.

[0146] The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

[0147] These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

[0148] WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 µM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro	
Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

[0149] These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

[0150] The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 µM) concractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro	
Prodrug	IC_{50} [nM]
(+) HO-/-OH	20
(-) HO-/-OH	680
(+) HO-/-OiBut	57
(+) HO-/-OBz	180
(+) BzO-/-OBz	220
(+) AcO-/-OiBut	240

[0151] These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

[0152] Different compounds of the invention were tested for their ability to penetrate the human skin (200 µm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV detection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin	
Prodrug	Flux rate [µg/cm²/24hrs]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

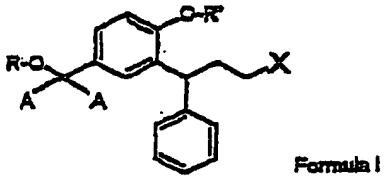
[0153] Disubsticution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

[0154] Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

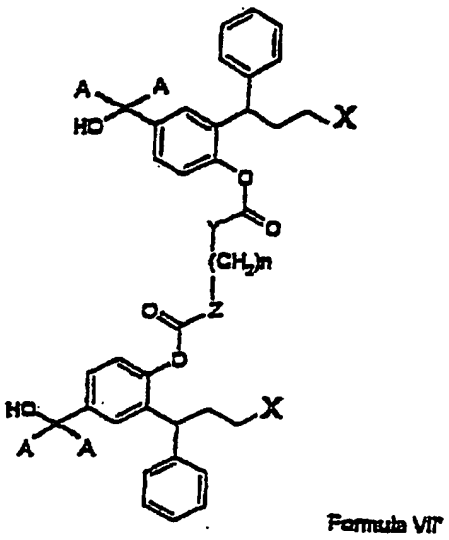
[0155] Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



Formula VII'

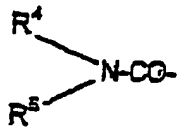
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

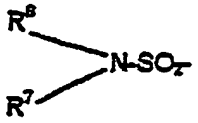
c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)



wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)

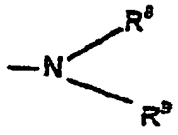


wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

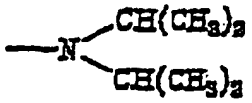
with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,
X represents a tertiary amino group of formula Ia



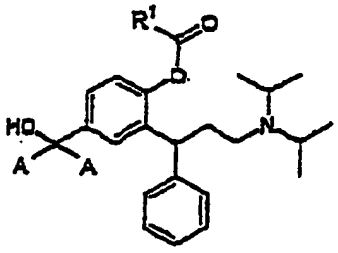
Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,
A represents hydrogen (^1H) or deuterium (^2H),
n is 0 to 12
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

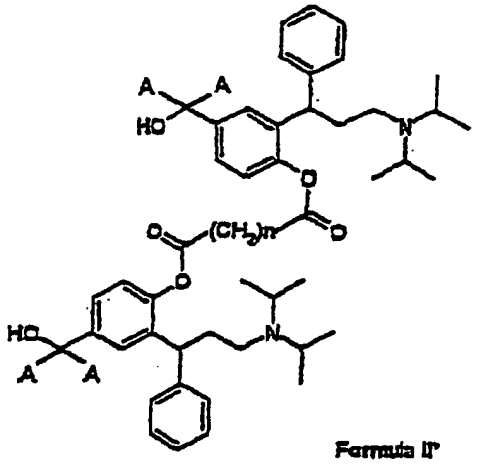
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

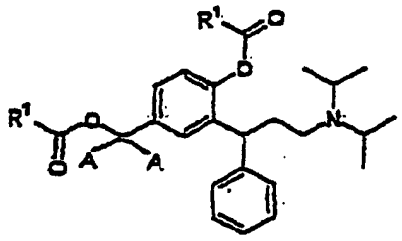
wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from :

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclopentanecarboxylic acid 2-(3-diisopronylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



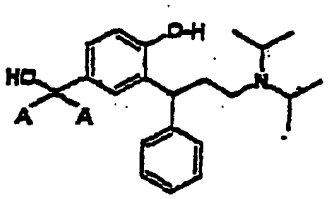
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:

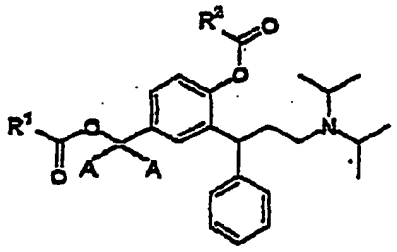
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula



wherein A is as defined in claim 1.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



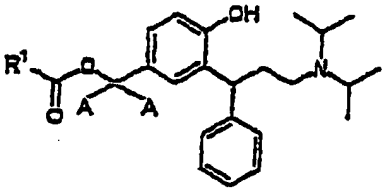
Formula IV

wherein R^1 is defined as in claim 3
and
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl
with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



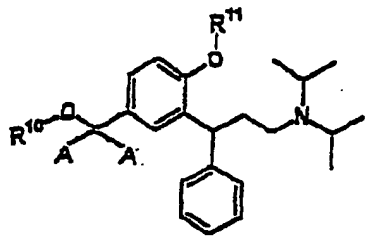
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



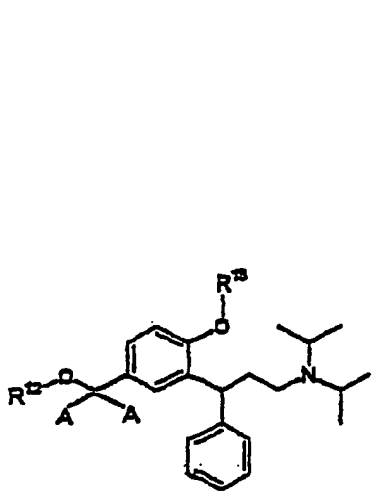
Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or -$SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

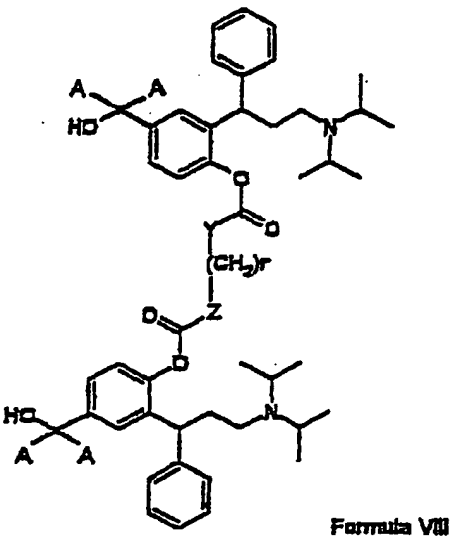
12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±) - [3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

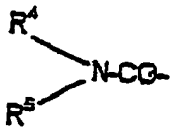


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



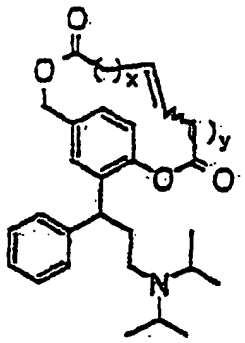
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:

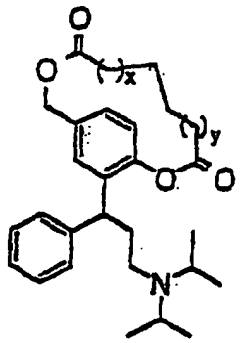
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±) - [2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3- (3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl) -4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



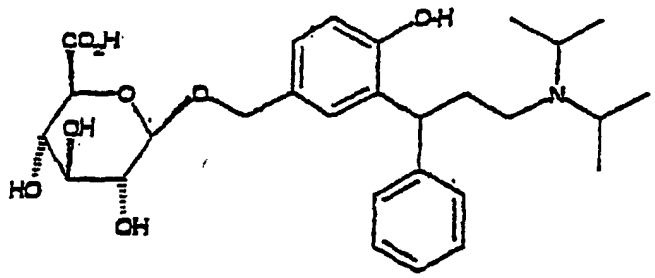
Formula IX'

wherein x and y are the same or different and represent the number of methylene units { CH_2 } and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

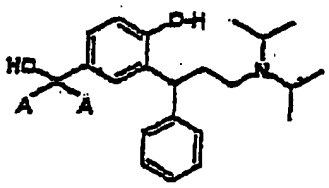


(v) (±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

(vi) cyclic oct-4-ene-1,8-dioate of Intermediate B,

(vii) cyclic octane-1,8-dioate of Intermediate B,

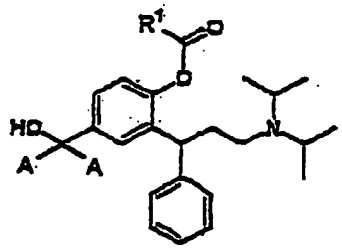
said Intermediate B having the formula



wherein A is as defined in claim 1

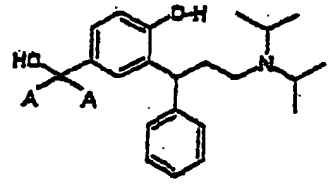
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

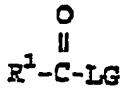


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

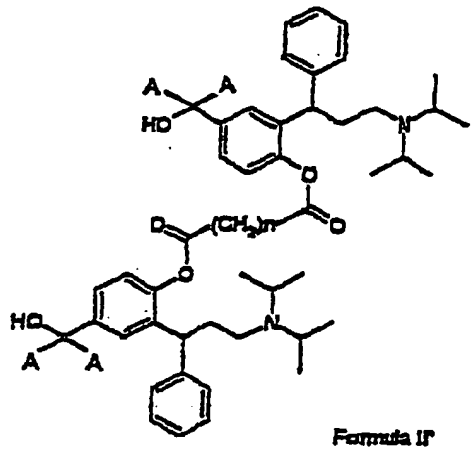


with an equivalent of an acylating agent selected from



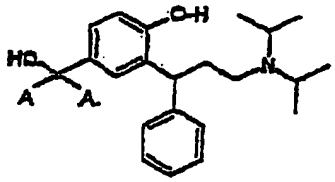
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

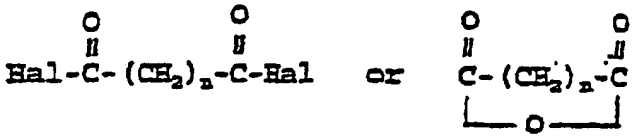


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

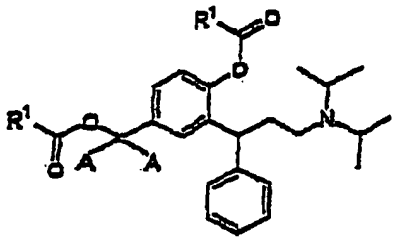


with an acylating agent selected from



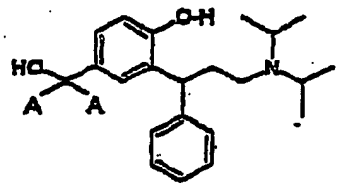
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



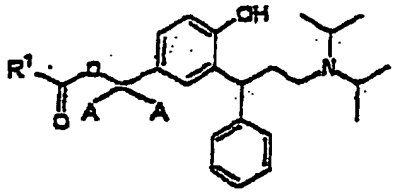
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



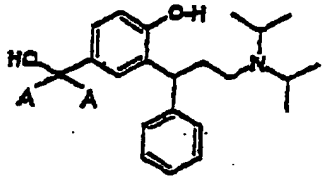
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



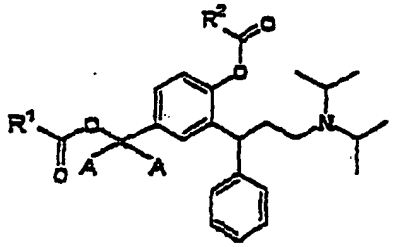
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



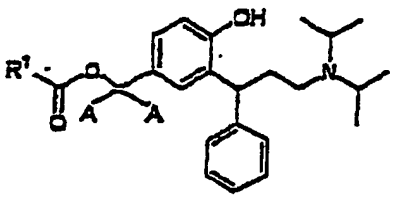
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

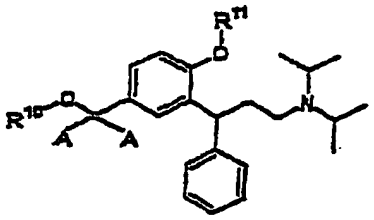
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

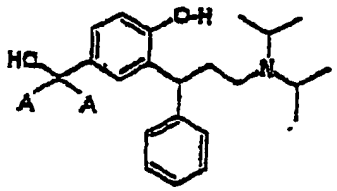
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



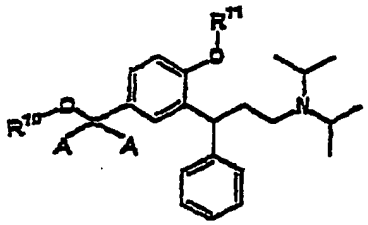
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



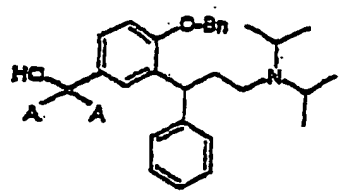
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

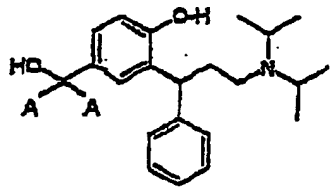


Formula VI

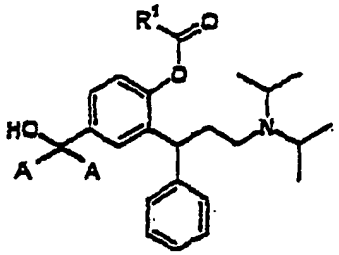
wherein R^{10} and R^{31} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

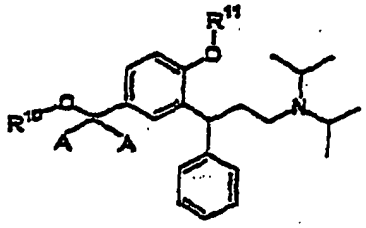


and



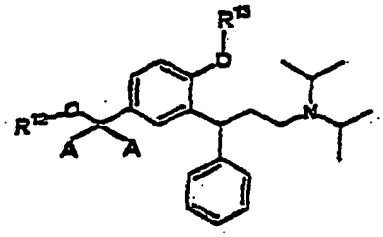
Formula II

or



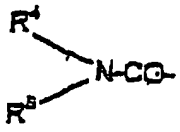
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined in claim 11 or

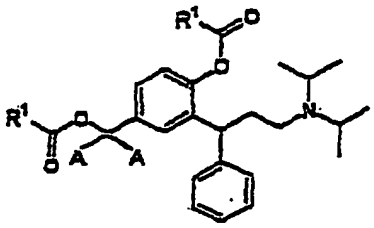


Formula VII

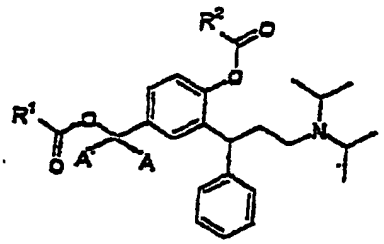
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



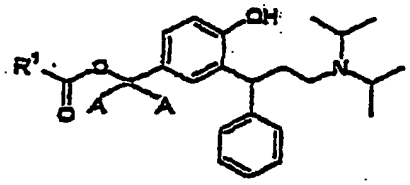
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



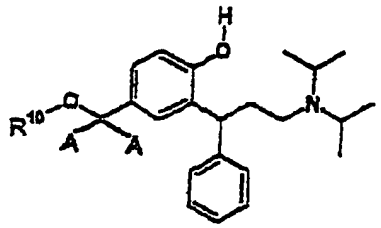
Formula IV



Formula V

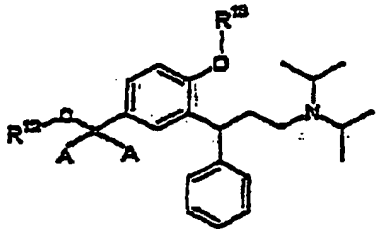
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

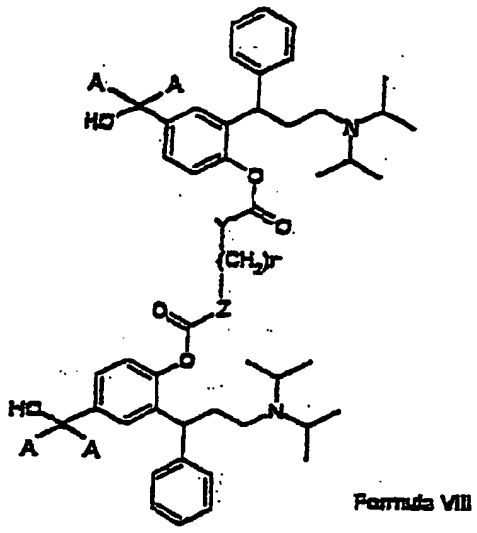


with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

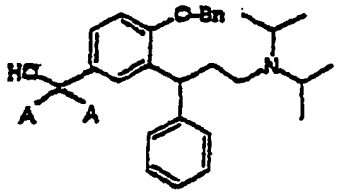


Formula VII

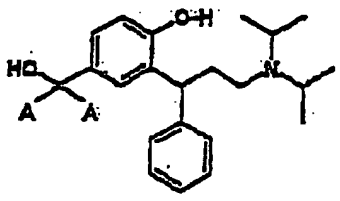


Formula VIII

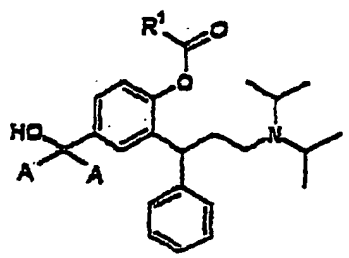
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



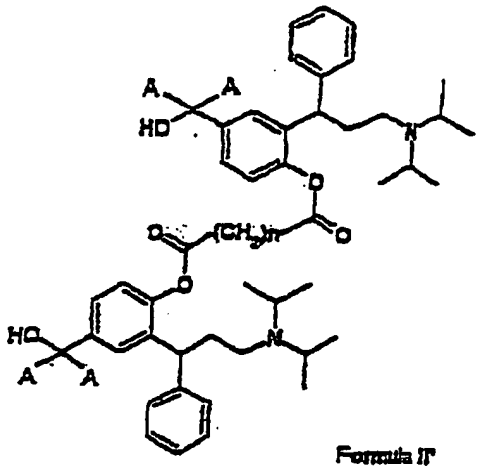
Intermediate A



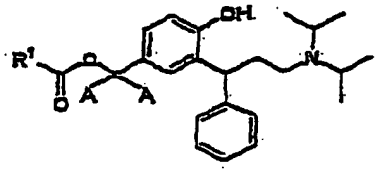
Intermediate B



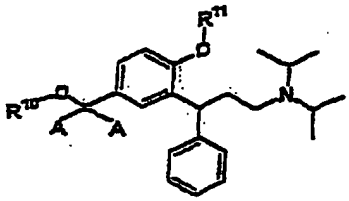
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

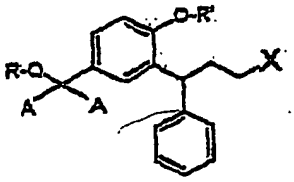
26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. A pharmaceutical composition as claimed in claim 26 which is a patch formulation.

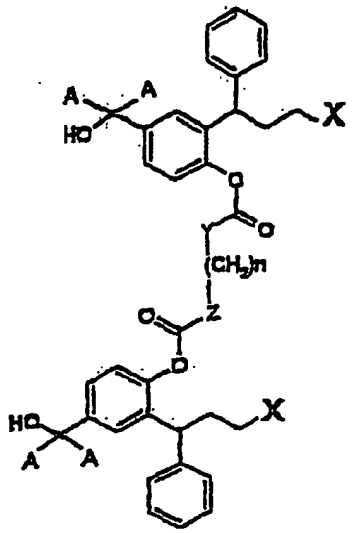
28. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

Patentansprüche

1. 3,3-Diphenylpropylamine der allgemeinen Formeln I und VII'



Formel I



Formel VII'

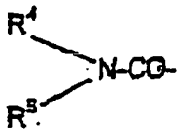
worin R und R' unabhängig ausgewählt sind aus

a) Wasserstoff, C_1-C_6-Alkyl, C_3-C_{10}-Cycloalkyl, substituiertem oder unsubstituiertem Benzyl, Allyl oder Kohlenhydrat; oder

b) Formyl, C_1-C_6-Alkylcarbonyl, Cycloalkylcarbonyl, substituiertem oder unsubstituiertem Arylcarbonyl, bevorzugt Benzoyl; oder

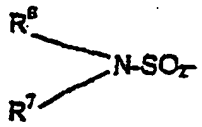
c) C_1-C_6-Alkoxycarbonyl, substituiertem oder unsubstituiertem Aryloxycarbonyl, Benzoylacyl, Benzoylglycyl, substituierten oder unsubstituierten Aminosäureresten; oder

d)



worin R^4 und R^5 unabhängig Wasserstoff, C_1-C_6-Alkyl, substituiertes oder unsubstituiertes Aryl, bevorzugt substituiertes oder unsubstituiertes Phenyl, Benzyl oder Phenoxyalkyl, worin der Alkylrest 1 bis 4 Kohlenstoffatome enthält, bedeuten und worin R^4 und R^5 zusammen mit dem Aminstickstoff einen Ring bilden können; oder

e)

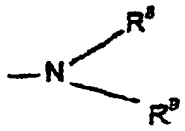


worin R^6 und R^7 unabhängig C_1-C_6-Alkyl, substituiertes oder unsubstituiertes Aryl, bevorzugt substituiertes oder unsubstituiertes Phenyl, Benzyl oder Phenoxyalkyl, worin der Alkylrest 1 bis 6 Kohlenstoffatome enthält, bedeuten; oder

f) einer Estergruppierung von anorganischen Säuren,

g) $-SiR_aR_bR_c$, worin R_a, R_b, R_c unabhängig ausgewählt sind aus C_1-C_4-Alkyl oder Aryl, bevorzugt Phenyl,

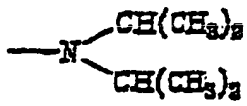
mit der Maßgabe, dass R' nicht Wasserstoff, Methyl oder Benzyl bedeutet, wenn R Wasserstoff bedeutet, R nicht Ethyl bedeutet, wenn R' Wasserstoff bedeutet,
X eine tertiäre Aminogruppe der Formel Ia



Formel Ia

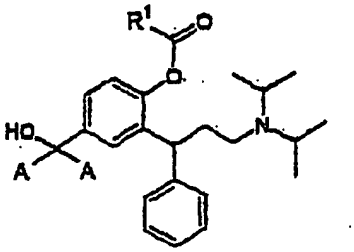
worin R^8 und R^9 nicht-aromatische Hydrocarbylgruppen, die gleich oder unterschiedlich sein können, bedeuten und die zusammen mindestens drei Kohlenstoffatome enthalten und worin R^8 und R^9 zusammen mit dem Aminstickstoff einen Ring bilden können, bedeutet,
Y und Z unabhängig eine Einfachbindung zwischen der $(CH_2)_n$-Gruppe und der Carbonylgruppe, O, S oder NH bedeuten,
A Wasserstoff (^1H) oder Deuterium (^2H) bedeutet,
n 0 bis 12 bedeutet
und
ihre Salze mit physiologisch annehmbaren Säuren, ihre freien Basen und wenn die Verbindungen in Form optischer Isomeren vorliegen, die racemischen Gemische und die individuellen Enantiomeren.

2. 3,3-Diphenylpropylamine nach Anspruch 1, worin X

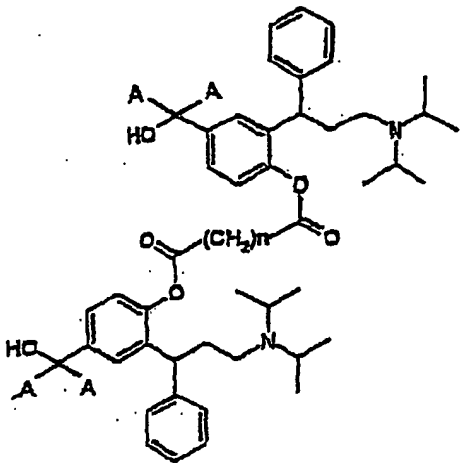


bedeutet.

3. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Phenolmonoestern, dargestellt durch die allgemeinen Formeln II und II'



Formel II



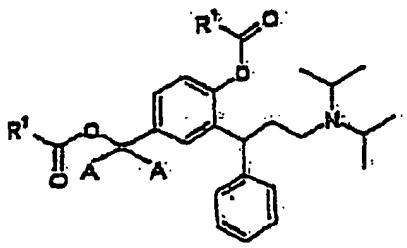
Formel II'

worin R^1 Wasserstoff, C_1-C_6-Alkyl oder Phenyl bedeutet.

4. 3,3-Diphenylpropylamine wie in Anspruch 3 beansprucht, ausgewählt aus:

(±)-Ameisensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Propionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-n-Buttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
R-(+)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2,2-Dimethylpropionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Acetamidoessigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Cyclopentancarbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Cyclohexancarbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
R-(+)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Methylbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Methylbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Acetoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-1-Naphthoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Naphthoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Chlorbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Methoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Methoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Nitrobenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Nitrobenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Malonsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Bernsteinsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Pentandionsäure-bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Hexandionsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester.

5. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus identischen Diestern, dargestellt durch die allgemeine Formel III



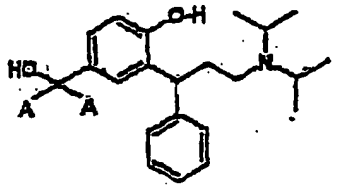
Formel III

worin R^1 die in Anspruch 3 gegebene Definition besitzt.

6. 3,3-Diphenylpropylamine nach Anspruch 5, ausgewählt aus:

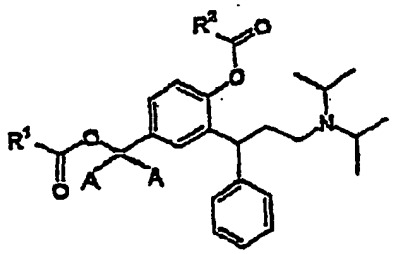
(±)-Ameisensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Essigsäure-4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Propionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenylester,
(±)-n-Buttersäure-4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenylester,
(±)-2,2-Dimethylpropionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)benzylester,
(±)-Benzoesäure-4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
R-(+)-Henzoesäure-4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,

Poly-co-DL-Lactiden des Zwischenprodukts B, wobei das Zwischenprodukt B die Formel



besitzt, worin A die in Anspruch 1 gegebene Definition besitzt.

7. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus gemischten Diestern, dargestellt durch die allgemeine Formel IV



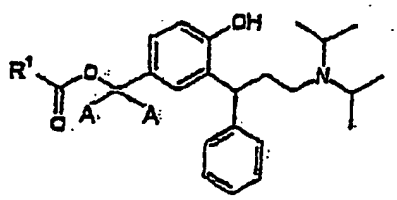
Formel IV

worin R^1 die in Anspruch 3 gegebene Definition besitzt
und
R^2 Wasserstoff, C_1-C_6-Alkyl oder Phenyl bedeutet,
mit der Maßgabe, dass R^1 und R^2 nicht identisch sind.

8. 3,3-Diphenylpropylamine nach Anspruch 7, ausgewählt aus:

(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenylester,
R-(+)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenylester,
(±)-Isobuttersäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
R-(+)-Isobuttersäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-2,2-Dimethylpropionsäure-4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-2,2-dimethylpropionsäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-Benzoesäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester.

9. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Benzylsäuremonoestern, dargestellt durch die allgemeine Formel V



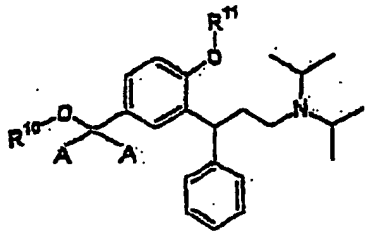
Formel V

worin R^1 die in Anspruch 3 gegebene Definition besitzt.

10. 3,3-Diphenylpropylamine nach Anspruch 9, ausgewählt aus:

(±)-Ameisensäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Essigsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Propionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Buttersäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Isobuttersäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-2,2-Dimethylpropionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Benzoesäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hyroxybenzylester.

11. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Ethern und Silylethern, dargestellt durch die allgemeine Formel VI



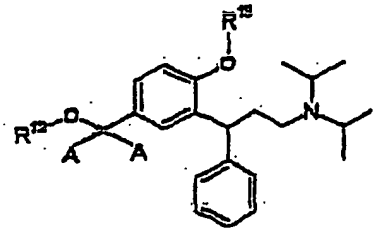
Formel VI

worin mindestens einer von R^{10} und R^{11} ausgewählt ist aus C_1-C_6-Alkyl, Benzyl oder $-SiR_aR_bR_c$, wie in Anspruch 1 definiert, und der andere von R^{10} und R^{11} zusätzlich Wasserstoff, C_1-C_6-Alkylcarbonyl oder Benzoyl bedeuten kann.

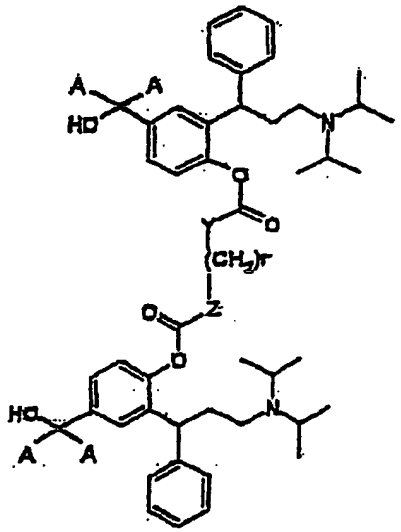
12. 3,3-Diphenylpropylamine nach Anspruch 11, ausgewählt aus:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenylester,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenylester,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]amin,
(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol,
(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenyl]propylamin,
(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenyl]propylamin,
(±)-[4-(tert.-Butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenyl]methanol,
(±)-Essigsäure-4-(tert.-butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-4-(tert.-Butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenol,
(±)-Essigsäure-4-(tert.-butyldimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-{3-[2-(tert.-Butyldimethylsilanyloxy)-5-(tert.-butyldimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}diisopropylamin,
(±)-[4-(tert.-Butyldiphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenyl]methanol,
(±)-Essigsäure-4-(tert.-butyldiphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-4-(tert.-Butyldiphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenol,
(±)-{3-[2-(tert.-Butyldiphenylsilanyloxy)-5-(tert.-butyldiphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}diisopropylamin,
(±)-Essigsäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Benzoesäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Isobuttersäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)phenol.

13. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Carbonaten und Carbamaten, dargestellt durch die allgemeinen Formeln VII und VIII

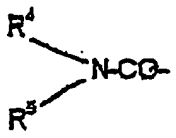


Formel VII



Formel VIII

worin Y, Z und n die in Anspruch 1 gegebenen Bedeutungen besitzen und worin R^{12} und R^{13} eine C_1-C_6-Alkoxycarbonylgruppe oder



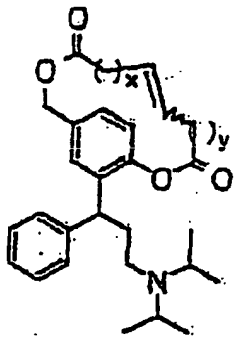
bedeuten, worin R^4 und R^5 die in Anspruch 1 gegebenen Bedeutungen besitzen.

14. 3,3-Diphenylpropylamine nach Anspruch 13, ausgewählt aus:

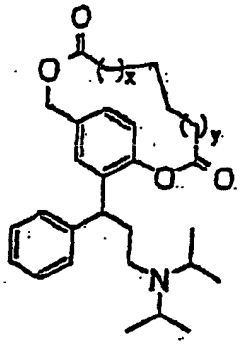
(±)-N-Ethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N,N-Dimethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N,N-Diethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N-Phenylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]essigsäureethylesterhydrochlorid,
(±)-N-Ethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzylester,
(±)-N,N-Dimethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzylester,
(±)-N,N-Diethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzylestern,
(±)-N-Phenylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzylester,
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]butyl}carbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylesterethylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylesterphenylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenylesterethylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenylesterphenylester.

15. 3,3-Diphenylpropylamine, ausgewählt aus

(i) Verbindungen der Formeln IX und IX'



Formel IX



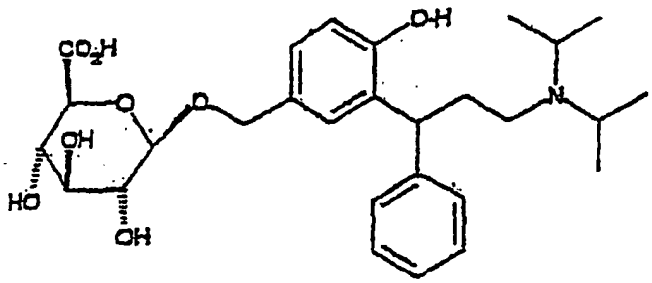
Formel IX'

worin x und y gleich oder unterschiedlich sind und die Zahl der Methyleneinheiten { CH_2 } bedeuten und im Bereich von 0 bis 6 liegen können,

(ii) (±) -Benzoesäure-2- (3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethylphenylester,

(iii) Poly-co-DL-Lactiden von 2- (3-Diisopropylaminophenylpropyl)-4-hydroxymethylphenol,

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-Dglucuronosyloxymethyl)phenol der Formel

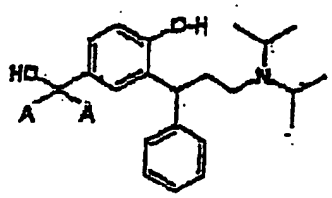


(v) (±)-Pent-4-ensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)phenylester,

(vi) cyclischem Oct-4-en-1,8-dioat des Zwischenprodukts B,

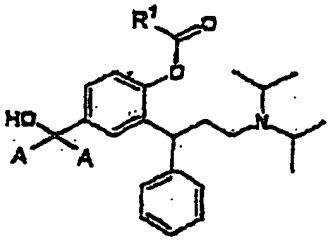
(vii) cyclischem Octan-1,8-dioat des Zwischenprodukts B,

wobei das Zwischenprodukt B die Formel



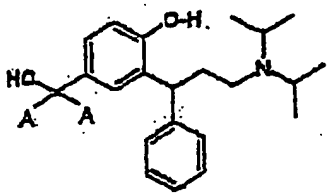
besitzt, worin A die in Anspruch 1 gegebene Definition besitzt
und
ihre Salze mit physiologisch annehmbaren Säuren, ihre freien Basen und, wenn die Verbindungen in Form optischer Isomeren vorliegen, das racemische Gemisch und die individuellen Enantiomeren.

16. Verfahren zur Herstellung von Phenolmonoestern, dargestellt durch die allgemeine Formel II

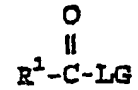


Formel II

wie in Anspruch 3 definiert, umfassend die Behandlung einer Verbindung der Formel

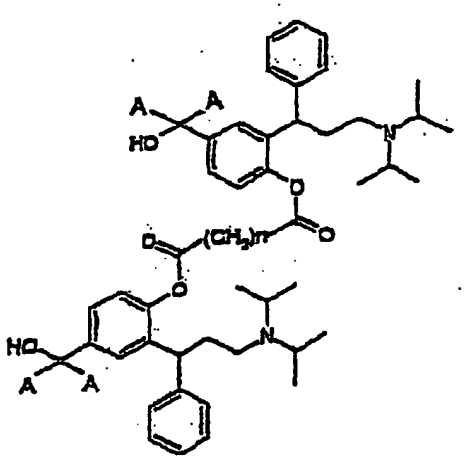


mit einem Äquivalent eines Acylierungsmittels, ausgewählt aus



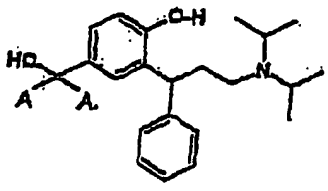
worin LG eine Austrittsgruppe, ausgewählt aus Halogenid, Carboxylat und Imidazolid, bedeutet und R^1 die in Anspruch 3 gegebenen Definitionen besitzt, in einem inerten Lösungsmittel in Anwesenheit eines Kondensationsmittels.

17. Verfahren zur Herstellung von Phenolmonoestern, dargestellt durch die allgemeine Formel II'

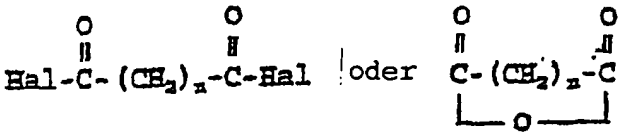


Formel II'

wie in Anspruch 3 definiert, umfassend die Behandlung von zwei Äquivalenten einer Verbindung der Formel

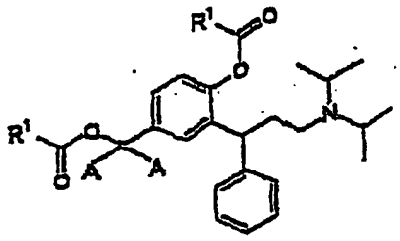


mit einem Acylierungsmittel, ausgewählt aus



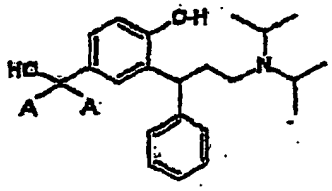
worin Hal ein Halogenatom bedeutet.

18. Verfahren zur Herstellung identischer Diester, dargestellt durch die allgemeine Formel III



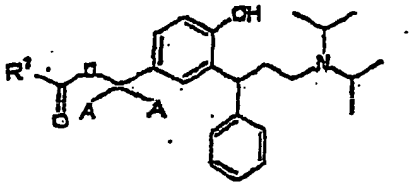
Formel III

wie in Anspruch 5 definiert, umfassend die Behandlung einer Verbindung der Formel



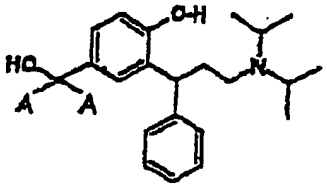
mit mindestens zwei Äquivalenten des Acylierungsmittels wie in Anspruch 16 definiert.

19. Verfahren zur Herstellung von Benzylsäuremonoestern, dargestellt durch die allgemeine Formel V



Formel V

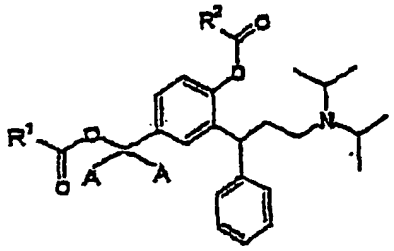
wie in Anspruch 9 definiert, umfassend die Behandlung einer Verbindung der Formel



bei Raumtemperatur und unter wasserfreien Bedingungen mit aktivierten Estern in Anwesenheit von Enzymen,

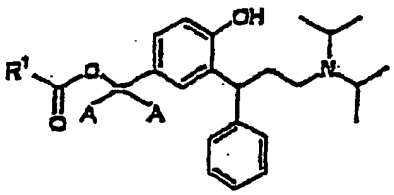
ausgewählt aus Lipasen oder Esterasen.

20. Verfahren zur Herstellung gemischter Diester, dargestellt durch die allgemeine Formel IV



Formel IV

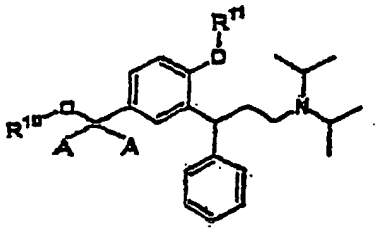
wie in Anspruch 7 definiert, umfassend die Acylierung eines Benzylsäuremonoesters, dargestellt durch die allgemeine Formel V



Formel V

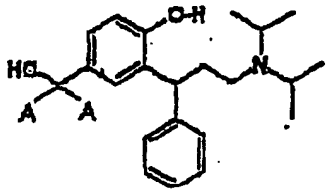
wie in Anspruch 9 definiert, oder eines Phenolmonoesters, dargestellt durch die Formel II, wie in Anspruch 3 definiert.

21. Verfahren zur Herstellung von Ethern, dargestellt durch die allgemeine Formel VI



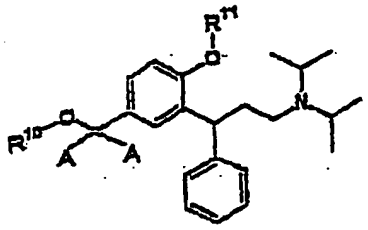
Formel VI

wie in Anspruch 11 definiert, worin R^{11} Wasserstoff bedeutet, umfassend die Umsetzung einer Verbindung der Formel



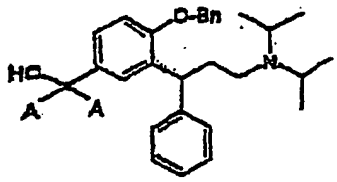
mit einem Alkohol R^{10}-OH in Anwesenheit eines Veresterungskatalysators.

22. Verfahren zur Herstellung von Ethern, dargestellt durch die allgemeine Formel VI

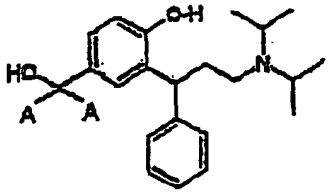


Formel VI

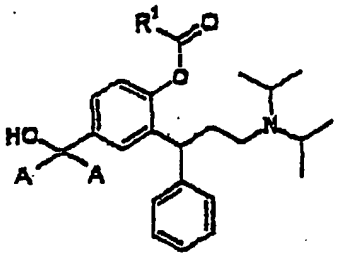
worin R^{10} und R^{11} die in Anspruch 11 gegebenen Definitionen besitzen, umfassend die Säure- oder Basenbehandlung von freien Benzylalkoholen, ausgewählt aus



und

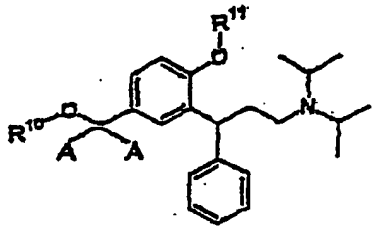


und



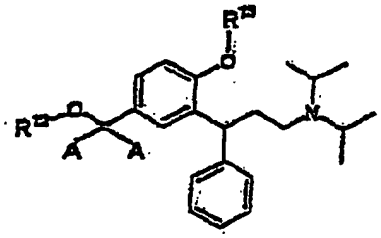
Formel II

oder



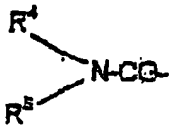
Formel VI

worin R^{10} Wasserstoff bedeutet und R^{11} die in Anspruch 11 gegebene Bedeutung besitzt, oder

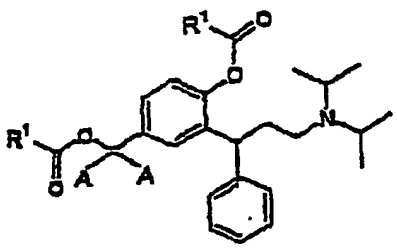


Formel VII

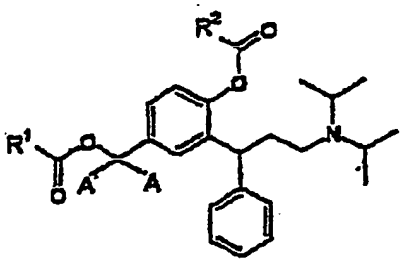
worin R^{12} Wasserstoff bedeutet und R^{13} eine C_1-C_6-Alkoxycarbonylgruppe bedeutet, oder



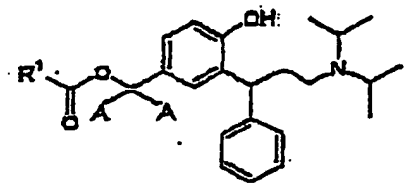
worin R^4 und R^5 die in Anspruch 1 gegebene Bedeutung besitzen, oder von benzylischen Acylaten, ausgewählt aus



Formel III



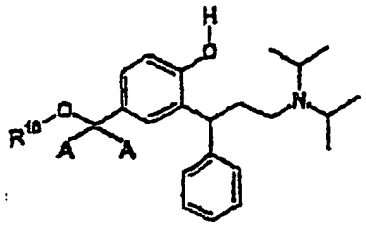
Formel IV



Formel V

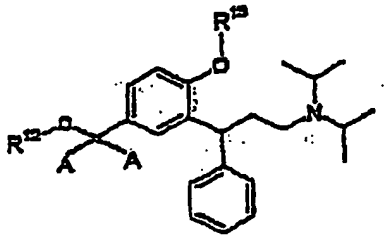
worin R^1 und R^2 die in Anspruch 7 gegebene Bedeutung besitzen, in Anwesenheit geeigneter Hydroxyreagentien.

23. Verfahren zur Herstellung von Ethern der Formel VI, wie in Anspruch 11 definiert, umfassend die Behandlung einer Verbindung der Formel

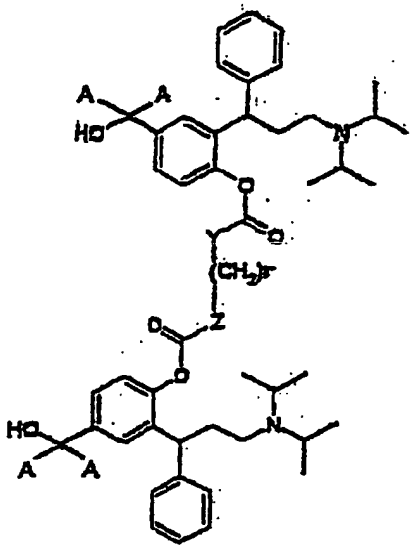


mit einem Alkylierungsmittel, ausgewählt aus Alkylhalogeniden, Alkylsulphaten und Alkyltriflaten, wobei die Alkylgruppe 1 bis 6 Kohlenstoffatome enthält.

24. Verfahren zur Herstellung von Carbonaten und Carbamaten, dargestellt durch die allgemeinen Formeln VII und VIII

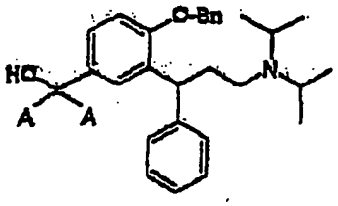


Formel VII

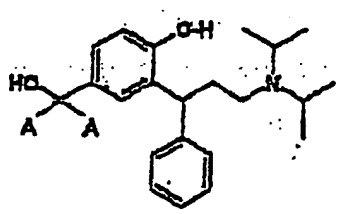


Formel VIII

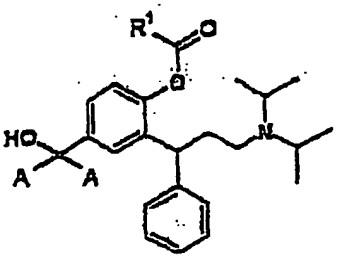
wie in Anspruch 13 definiert, umfassend die Umsetzung einer Verbindung, ausgewählt aus der Gruppe bestehend aus



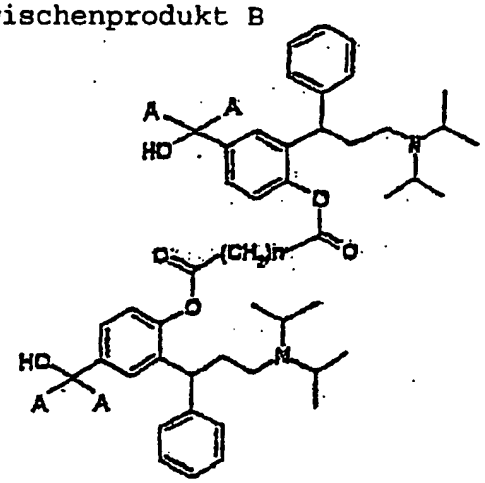
Zwischenprodukt A



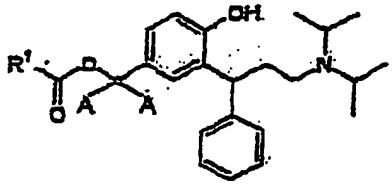
Zwischenprodukt B



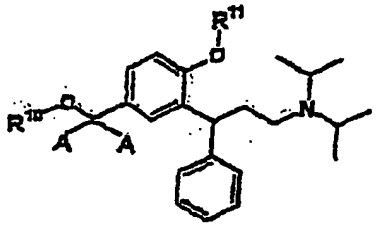
Formel II



Formel II'



Formel V



Formel VI

worin R^1 wie in Anspruch 3 definiert ist, n 0 bis 12 bedeutet, Bn Benzyl bedeutet, einer der Substituenten R^{10} oder R^{11} Wasserstoff bedeutet und der andere die in Anspruch 11 gegebene Definition besitzt, mit aktivierten Carbonylverbindungen oder Carbonyl-Vorstufereagentien, ausgewählt aus Haloformiaten, Ketenen, aktivierten Estern, gemischten Anhydriden von organischen oder anorganischen Säuren, Isocyanaten und Isothiocyanaten.

25. 3,3-Diphenylpropylamine nach den Ansprüchen 1 bis 15 für die Verwendung als pharmazeutisch aktive Substanzen, insbesondere als antimuskarinische Mittel.

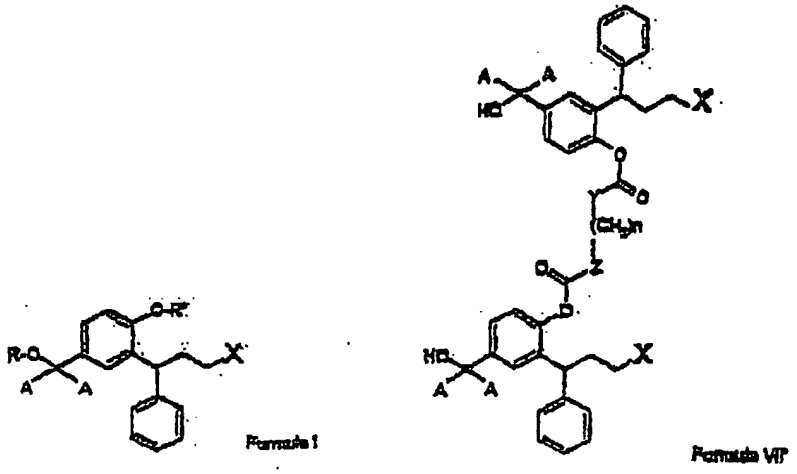
26. Pharmazeutische Zubereitung, umfassend ein 3,3-Diphenylpropylamin, wie in einem der Ansprüche 1 bis 15 definiert, und einen pharmazeutisch verträglichen Träger.

27. Pharmazeutische Zubereitung nach Anspruch 26, die eine Plättchen- bzw. Pflaster-Zubereitung ist.

28. Verwendung von 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 15 zur Herstellung eines antimuskarinischen Arzneimittels.

Revendications

1. 3,3-Diphénylpropylamines de formules générales I et VII' :

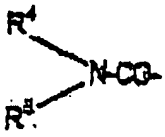


Formule I

Formule VII'

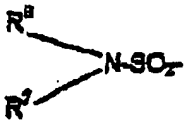
dans lesquelles R et R' sont indépendamment choisis à partir

a) d'un atome d'hydrogène, d'un groupement alkyle C_1-C_6, d'un groupement cycloalkyle C_9-C_{10}, d'un benzyle substitué ou non substitué, d'un groupement allyle ou d'un carbohydrate ; ou
b) d'un groupement formyle, d'un groupement alkylcarbonyle C_1-C_6, d'un cycloalkylcarbonyle, d'un arylcarbonyle substitué ou non substitué, de préférence le benzoyle ; ou
c) d' un groupement alkoxycarbonyle C_1-C_6, d'un aryloxycarbonyle substitué ou non substitué, d'un benzoylacyle, d'un benzoylglycyle, d'un résidu d'aminoacide substitué ou non substitué ; ou
d)



dans lequel R^4 et R^5

représentent indépendamment un atome d'hydrogène, un groupement alkyle C_1-C_6, un groupement aryle substitué ou non substitué, de préférence un phényle substitué ou non substitué, un groupement benzyle ou un phénoxyalkyle dans lequel le résidu alkyle a 1 à 4 atomes de carbone et dans lequel R^4 et R^5 peuvent former un cycle ainsi que l'azote de l'amine ; ou
e)



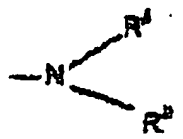
dans lequel R^6 et R^7

représentent indépendamment un groupement alkyle C_1-C_6, un groupement aryle substitué ou non substitué, de préférence un phényle substitué ou non substitué, un groupement benzyle ou un phénoxyalkyle dans

lequel le résidu alkyle a 1 à 6 atomes de carbone ; ou
f) un groupement ester d'acides inorganiques,
g) $-SiR_aR_bR_c$ dans lequel R_a, R_b, R_c sont indépendamment choisis parmi un groupement alkyle C_1-C_4 ou aryle, de préférence un groupement phényle,

à condition que R' ne soit ni un atome d'hydrogène, ni un groupement méthyle ou benzyle si R est un atome d'hydrogène, R n'est pas un groupement éthyle si R' est un atome d'hydrogène,

X représente un groupement amine tertiaire de formule Ia



Formule Ia

dans lequel R^8 et R^9 représentent des groupements d'hydrocarbyles non-aromatiques, qui peuvent être identiques ou différents et qui contiennent en même temps au moins trois atomes de carbone, et dans lesquels R^8 et R^9 peuvent former un cycle ainsi que l'azote de l'amine.

Y et Z représentent indépendamment une liaison simple entre le groupement $(CH_2)_n$ et le groupement carbonyle, O, S ou NH,

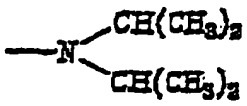
A représente un atome d'hydrogène (^1H) ou de deutérium (^2H),

n est compris entre 0 et 12

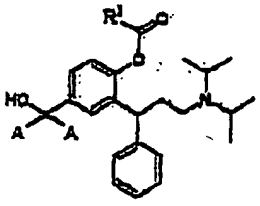
et

leurs sels avec des acides physiologiquement acceptables, leurs bases libres et, quand les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères uniques.

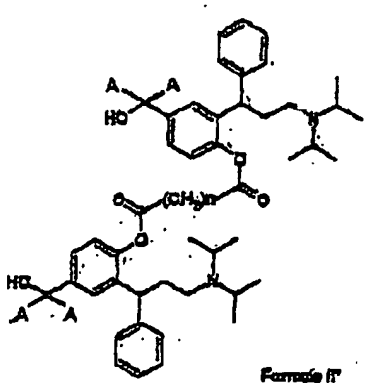
2. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 1, dans lesquelles X est



3. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi les monoesters phénoliques représentés par les formules générales II et II'



Formule II



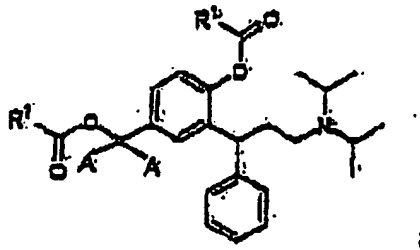
Formule II'

dans lesquelles R^1 représente un atome d'hydrogène, un alkyle C_1-C_6 ou un phényle.

4. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 3 choisies parmi :

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide formique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide propionique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide butyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide isobutyrique,
l'ester de R-(+)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide isobutyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-acétamidoacétique,
l'ester de (+) -2- (3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide cyclopentanecarboxyli-que,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide cyclohexanecarboxyli-que,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide benzoïque,
l'ester de R-(+)-2-(3-diisoproplamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide benzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-hydroxyméthylphényle de l'acide 4-méthylbenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-méthylbenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-acétoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 1-naphtoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-naphtoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 4-chlorobenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 4-méthoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-méthoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-hydroxyméthylphényle de l'acide 4-nitrobenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-nitrobenzoïque,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide malonique,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide succinique,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide pentanoïque,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide hexadioïque.

5. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi les diesters identiques à ceux représentés par la formule générale III



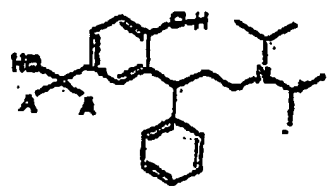
Formule III

dans laquelle R^1 est défini selon la revendication 3

6. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 5 choisies parmi :

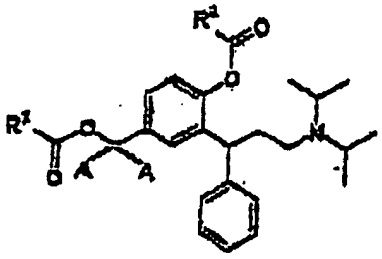
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide formique,

l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-propionyloxyméthylphényle de l'acide propionique,
l'ester de (±)4-n-butyryloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-phényle de l'acide n-butyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-isobutyryloxyméthylphényle de l'acide isobutyrique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-benzyle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-benzoyloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-phényle de l'acide benzoïque,
l'ester de R-(+)-4-benzoyloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-phényle de l'acide benzoïque,
les poly-co-DL-lactides de l'intermédiaire B, ledit intermédiaire B ayant la formule



dans laquelle A est défini selon la revendication 1

7. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des diesters mixtes représentées par la formule générale IV



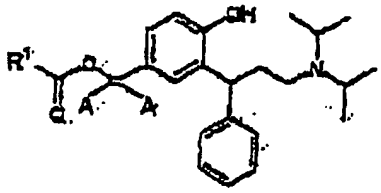
Formula IV

dans laquelle R^1 est défini selon la revendication 3
et
R^2 représente un atome d'hydrogène, un groupement alkyle C^1-C^6 ou un phényle
à condition que R^1 et R^2 ne soient pas identiques

8. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 7 choisies parmi

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide benzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-acétoxyméthylphényle de l'acide benzoïque,
l'ester de R-(+)-2-(3-diisopropylamino-1-phénylpropyl)-4-acétoxyméthylphényle de l'acide benzoïque,
l'ester de (±)-4-acétoxyméthyl-2-(3-diisopropylamino-1-phényl-propyl)-phényle de l'acide isobutyrique,
l'ester de R-(+)-4-acétoxyméthyl-2-(3-diisopropylamino-1-phényl-propyl)-phényle de l'acide isobutyrique,
l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phényl propyl)-benzyle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phényl propyl)-phényle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide benzoïque.

9. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des monoesters benzyliques représentés par la formule générale V



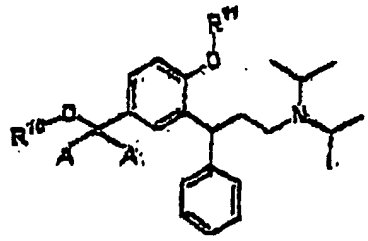
Formule V

dans laquelle R^1 est défini selon la revendication 3

10. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 9 choisies parmi

l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide formique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide acétique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide propionique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide butyrique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide isobutyrique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide 2,2-diméthylpropionique
l'ester de (±)-3- (3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide benzoïque

11. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des éthers et des éthers silylés représentées par la formule générale VI



Formule VI

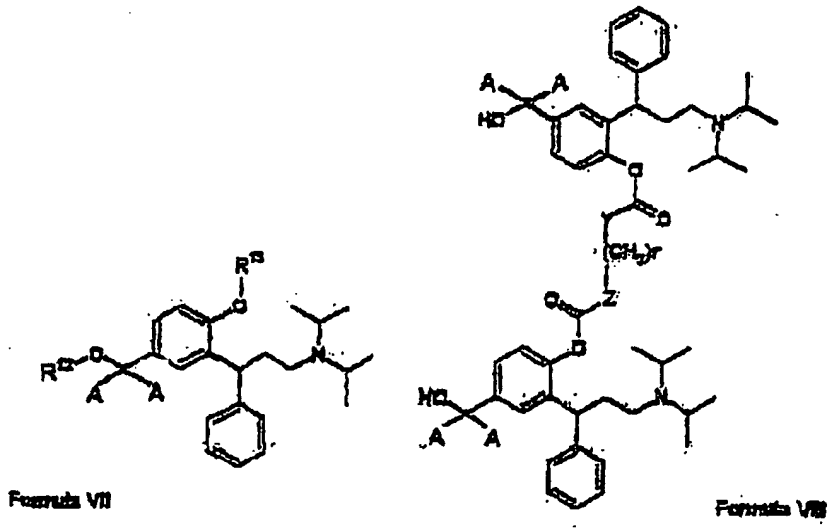
dans laquelle au moins un des substituants R^{10} ou R^{11} est choisi parmi un groupement alkyle C_1-C_6, un benzyle ou $-SiR_aR_bR_c$ selon la revendication 1 et l'autre substituant R^{10} ou R^{11} peut en plus représenter un atome d'hydrogène, un groupement alkyl carbonyle C_1-C_6 ou un benzoyle.

12. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 11 choisies parmi

le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-méthoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-propoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-isoprop-oxyméthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-butoxy-méthyl phénol,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-méthoxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxyméthylphényle de l'acide acétique,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-tri-méthylsilanyloxyméthyl phénol,
la (±)-diisopropyl-[3-phényl-3-(2-triméthylsilanyloxy-5-tri-méthylsilanyloxyméthyl)-propyl]-amine,
le (±)-[3-(3-diisopropylamino-1-phénylpropyl)-4-tri-méthylsilanyloxyphényl]-méthanol,
la (±)-diisopropyl-[3-(5-méthoxyméthyl-2-triméthyl-silanyloxyphényl)]-3-phénylpropyl-amine,
la (±)-diisopropyl-[3-(5-éthoxyméthyl-2-triméthyl sil-anyloxyphényl)]-3-phénylpropyl-amine,
le (±)-[4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phényl]-méthanol,
l'ester de (±)-4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,

le (±)-4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phénol,
l'ester de (±)-4-(sert.-butyl-diméthylsilanyloxy)-2-(3-diisopropylamino-1-phénylpropyl)-phényle de l'acide acétique,
la (±)-{3-[2-(tert.-butyl-diméthylsilanyloxy)-5-(tert.-butyl-diméthylsilanyloxyl)-phényl]-3-phényl propyl} di-iso-propylamine,
le (±)-[4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phényl]-méthanol,
l'ester de (±)-4-(tert.-butyl-diphéthylsilanyloxyméthyl)-2-(3-diisopropylamino-1-phénylpropyl)-phényle de l'acide acétique,
le (±)-4-(tert.-butyl-diphéthylsilanyloxyméthyl)-2-(3-diiso propylamino-1-phénylpropyl)-phénol,
la (±)-{3-[2-(tert.-butyl-diméthylsilanyloxy)-5-(tert. -butyl-diphéthylsilanyloxyméthyl)-phényl]-2-phényl-propyl} diisopropylamine,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide benzoïque,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phényl-propyl)-benzyle de l'acide isobutyrique,
le (±)-2-(3-diisopropylamino-1-phényl-propyl)-4-(1β-D-glucuronosyloxyméthyl)-phénol.

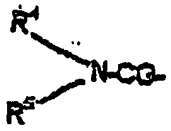
13. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des carbonates et des carbamates représentés par les formules générales VII et VIII



Formule VII

Formule VIII

dans lesquelles Y, Z et n sont définis selon la revendication 1 et dans lesquelles R^{12} et R^{13} représentent un groupement alcoxycarbonyle C_1-C_6 ou



dans lesquelles R^4 et R^5 sont définis selon la revendication 1

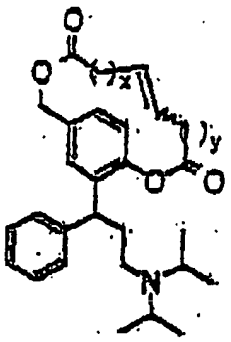
14. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 13 choisies parmi :

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N-éthylcarbamique,

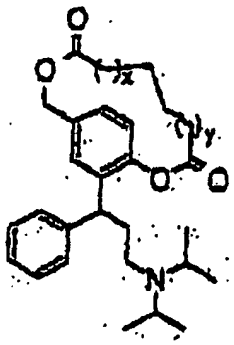
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N,N-diméthylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N,N-diéthylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N-phénylcarbamique,
l'ester de (±)-[2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphénoxycarbonylamino] éthyle du chlorhydrate de l'acide acétique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N-éthylcarbamoyloxybenzyle de l'acide N,éthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-N,N-di-méthylcarbamoyloxybenzyle de l'acide N,N-diméthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N, N-diéthylcarbamoyloxybenzyle de l'acide N,N-diéthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N-phénylcarbamoyloxybenzyle de l'acide N-phénylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide {4-[2-(3-diisopropyl amino-1-phénylpropyl)-4-hydroxyméthyl phénoxycarbonyl-amino]-butyl} carbamique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle et d'éthyle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxy-méthylphényle et de phényle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-éthoxy-carbonyloxyméthylphényle et d'éthyle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxy-carbonyloxyméthylphényle et de phényle de l'acide carbonique,

15. 3,3-Diphénylpropylamines choisies parmi :

(i) les composés de formules IX et IX'

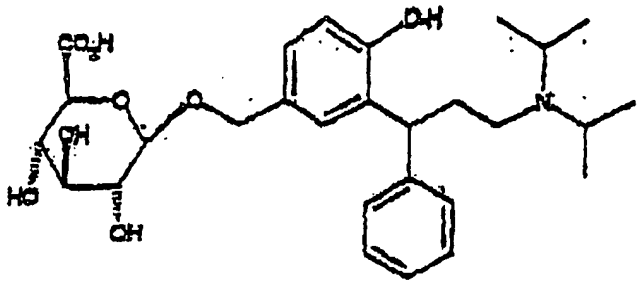


Formule IX



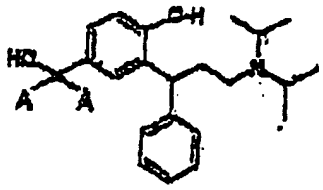
Formule IX'

dans lesquelles x et y sont identiques ou différents et représentent le nombre d'unités méthylènes -(CH_2)- et peuvent être compris entre 0 et 6,
(ii) l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxysulphooxyméthylphényle de l'acide benzoïque,
(iii) les poly-co-DL-lactides-2-(3-diisopropyl amino-1-phénylpropyl)-4-hydroxyméthyl-phénol,
(iv) le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-(1β-D-glucuronosyloxyméthyl)-phénol ayant la formule



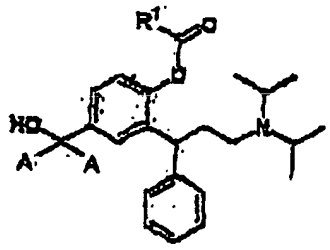
(v) l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4- (pent-4-enoyloxyméthyl) -phényle de l'acide pent-4-énoïque,
(vi) le 1,8-dioate d'oct-4-ène cyclique de l'intermédiaire B,
(vii) le 1,8-dioate d'octane cyclique de l'intermédiaire B

ledit intermédiaire B ayant la formule



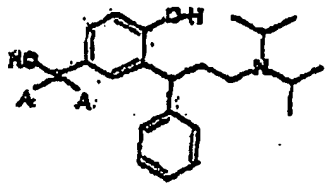
dans laquelle A est selon la revendication 1
et
leurs sels avec des acides physiologiquement acceptables, leurs bases libres et, quand les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères uniques.

16. Procédé pour la production de monoesters phénoliques représentés par la formule générale II



Formule II

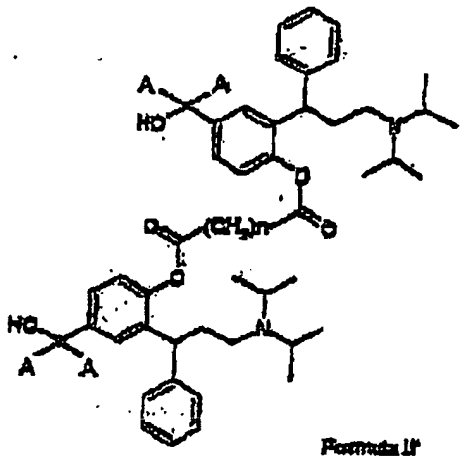
selon la revendication 3, qui comprend le traitement d'un composé de formule



avec un équivalent d'un agent acyclique choisi parmi

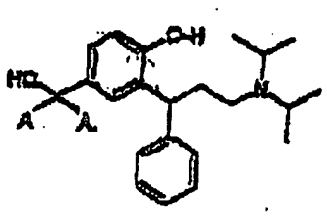
dans lequel LG représente un groupe partant choisi parmi les halogénures, les carboxylates et les imidazoles et R^1 est selon la revendication 3, dans un solvant inerte en présence d'un agent de condensation.

17. Procédé pour la production de monoesters phénoliques représentés par la formule générale II'

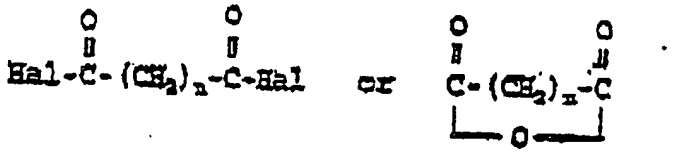


Formule II'

selon la revendication 3, qui comprend le traitement de deux équivalents d'un composés de formule

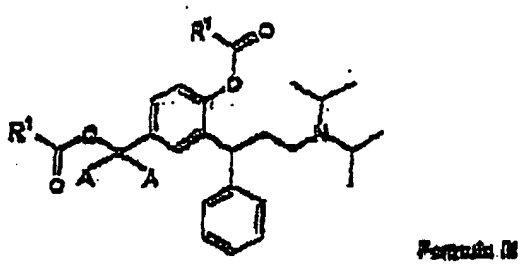


avec un agent d'acylation choisi parmi



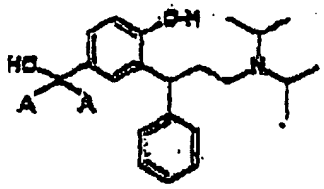
dans lequel Hal représente un atome d'halogène

18. Procédé pour la production de diesters identiques représentés par la formule générale III



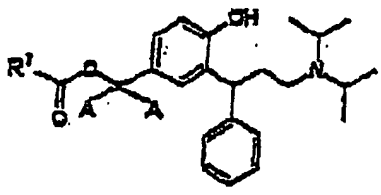
Formule III

selon la revendication 5, qui comprend le traitement d'un composé de formule



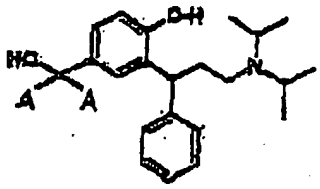
avec au moins deux équivalents d'un agent d'acylation selon la revendication 16.

19. Procédé pour la préparation de monoesters benzyliques représentés par la formule générale V



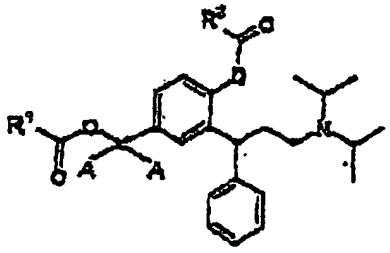
Formule V

selon la revendication 9, qui comprend le traitement d'un composé de formule



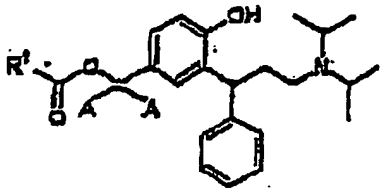
à température ambiante et dans des conditions anhydres avec des esters activés en présence d'enzymes choisies parmi les lipases et les ostérases.

20. Procédé pour la préparation de diesters mixtes représentés par la formule générale IV



Formula IV

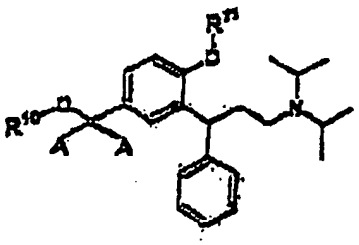
selon la revendication 7, qui comprend l'acylation d'un monoester benzylique représenté par la formule générale V



Formula V

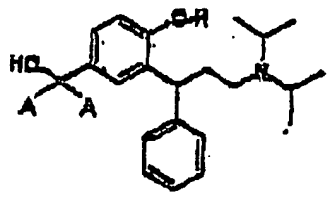
selon la revendication 9 ou par un monoester phénolique représenté par la formule II selon la revendication 3

21. Procédé de production d'éthers représentés par la formule générale VI



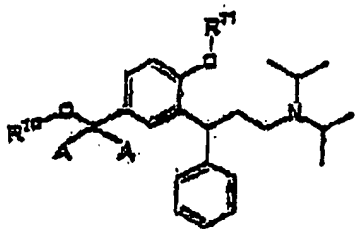
Formula VI

selon la revendication 11 dans laquelle R^{11} est un atome d'hydrogène qui comprend la réaction d'un composé de formule



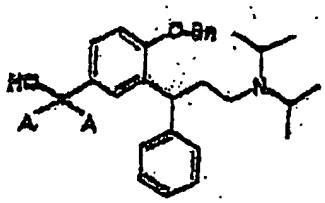
avec un alcool R^{10}-OH en présence d'un catalyseur d'estérification.

22. Procédé pour la préparation d'éthers représentés par la formule générale VI

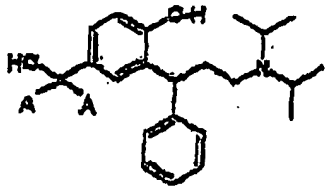


Formule VI

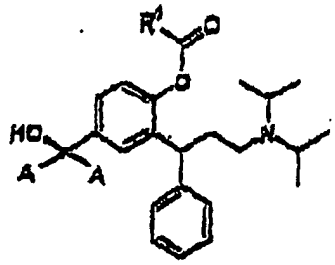
dans laquelle R^{10} et R^{11} sont selon la revendication 11, qui comprend un traitement acide ou basique d'alcools benzyliques libres choisis parmi



et

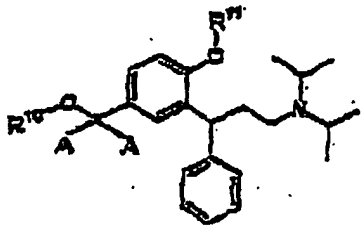


et



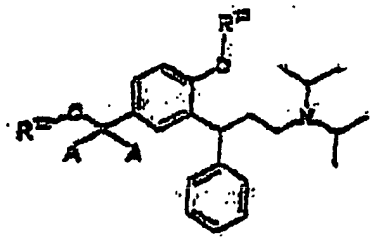
Formule V

ou



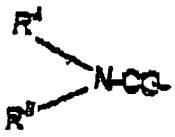
Formule VI

dans lesquelles R^{10} est un atome d'hydrogène et R^{11} est selon la revendication 11 ou

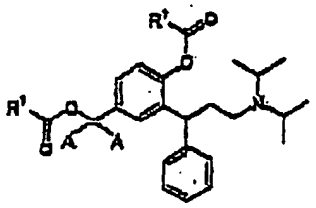


Formule VII

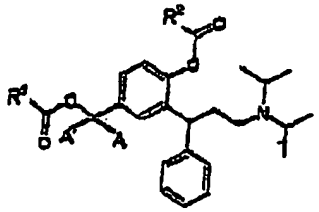
dans laquelle R^{12} est un atome d'hydrogène et R^{13} représente un groupement alcoxycarbonyle ou



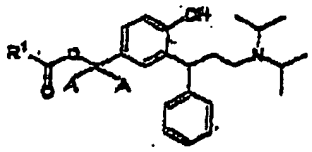
dans lequel R^4 et R^5 sont selon la revendication 1 ou des acylates benzyliques choisis parmi



Formule III



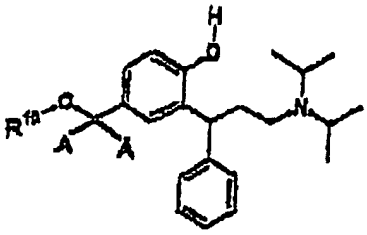
Formule IV



Formule V

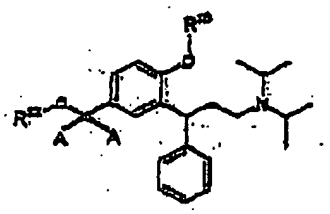
dans lesquels R^1 et R^2 sont selon la revendication 7 en présence de réactifs hydroxylés adéquats

23. Procédé pour la préparation d'éthers de formule VI selon la revendication 11, qui comprend le traitement d'un composé de formule

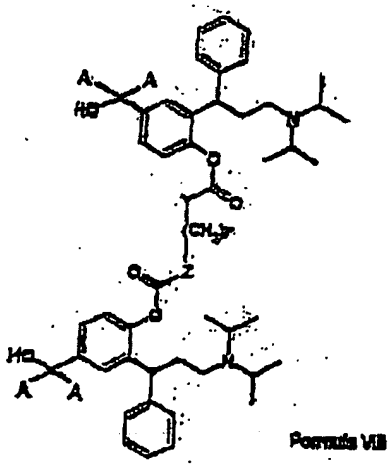


avec un agent d'alkylation choisi parmi les halogénures d'alkyle, les sulfates d'alkyle et les triflates d'alkyle, ledit groupe alkyle ayant 1 à 6 atomes de carbone.

24. Procédé pour la préparation de carbonates et de carbamates représentés par les formules générales VII et VIII

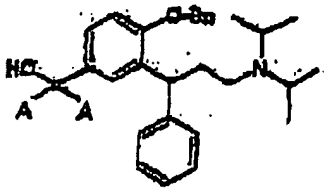


Formule VII

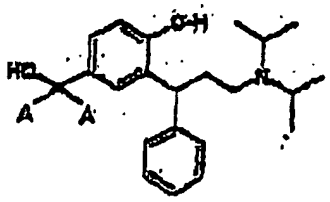


Formule VIII

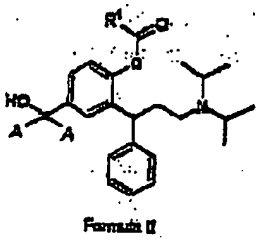
selon la revendication 13, qui comprend la réaction d'un composé choisi parmi le groupe constitué de

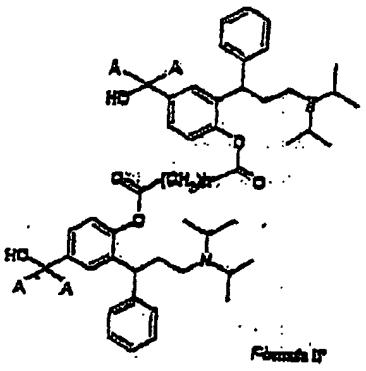


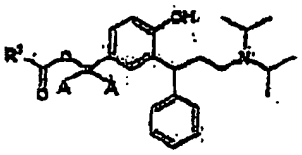
Intermédiaire A



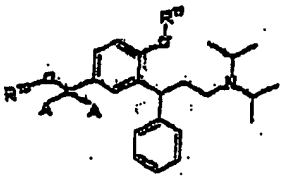
Intermédiaire B







Formule V



dans lequel R^1 est selon la revendication 3, n est compris entre 0 et 12, Bn est un groupement benzyle, l'un des substituants R^{10} et R^{11} est un atome d'hydrogène et l'autre est selon la revendication 11 avec des composés carbonylés activés ou des réactifs précurseurs de carbonyles choisis parmi les halogénoformates , les cétènes, les esters activés, les anhydrides mixtes d'acides organiques ou inorganiques, les isocyanates et les isothiocyanates.

25. 3,3-Diphénylpropylamines comme revendiquées dans les revendications 1 à 15 choisies pour un usage en tant que substances actives pharmaceutiques, surtout en tant qu'agents antimuscariniques.

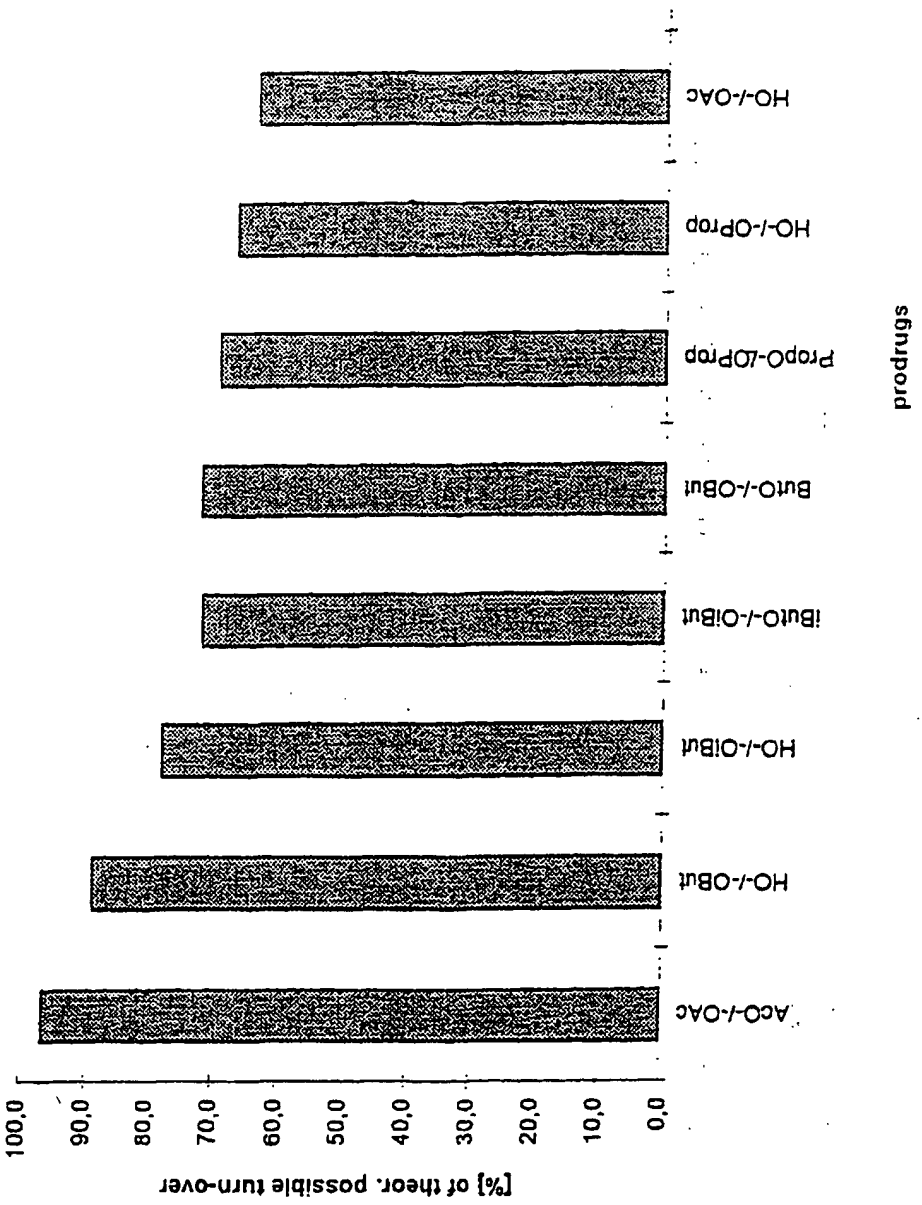
26. Compositions pharmaceutiques comprenant une 3,3-diphénylpropylamine comme revendiquée dans les revendications 1 à 15 et un support pharmaceutique compatible

27. Composition pharmaceutique comme revendiquée dans la revendication 26 qui est une formulation en pastille.

28. Utilisation d'une 3,3-diphénylpropylamine comme revendiquée dans les revendications 1 à 15 pour préparer un médicament antimuscarinique.

FIG. 1

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 128 819 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
20.08.2003 Bulletin 2003/34

(21) Application number: **99971702.8**

(22) Date of filing: **11.11.1999**

(51) Int Cl.[7]: **A61K 9/16**, A61K 9/26, A61K 9/58, A61K 31/135, A61P 13/10, A61P 1/00

(86) International application number:
PCT/SE99/02052

(87) International publication number:
WO 00/027364 (18.05.2000 Gazette 2000/20)

(54) **NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT**

NEUE KÜGELCHEN MIT KONTROLLIERTER FREISETZUNG, EIN VERFAHREN ZU DEREN HERSTELLUNG UND DIESE ENTHALTENDE FORMULIERUNG DES TYPS "MULTIPLE UNIT"

NOUVELLES PERLES A LIBERATION CONTROLEE, METHODE DE PRODUCTION, ET FORMULATION MULTICOUCHE COMPRENANT LEDIT COMPRIME

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **11.11.1998 SE 9803871**
26.08.1999 WOPCT/SE99/01463

(43) Date of publication of application:
05.09.2001 Bulletin 2001/36

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(56) References cited:
EP-A2- 0 061 217
WO-A1-96/01621
WO-A1-96/29992

EP 1 128 819 B1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] The present invention relates to pharmaceutical controlled release beads comprising a drug, to a formulation containing said controlled release beads, and to a method of preparing said beads.

[0002] A common type of controlled release beads comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer.

[0003] An example of such controlled release beads is described in US-A-5,783,215 where each bead comprises (i) a core unit of a soluble or insoluble inert material, (ii) a first layer on the core unit comprising an active ingredient dispersed in a hydrophilic polymer, (iii) an optional second layer of hydrophilic polymer covering the first layer, and (iv) an outermost membrane layer effective for controlled release of the active ingredient.

[0004] In the above and similar controlled release beads it is not uncommon to apply a "sealcoat" in the form of a small amount (e.g. 1-3%) of a water-soluble polymer, such as hydroxypropylmethyl cellulose (HPMC) or polyvinylpyrrolidone (PVP), between the inert core and the layer containing the active ingredient. The purpose thereof is generally to isolate the drug from the core surface in the event that a drug-core chemical interaction is possible, and/or to smooth the surface of the inert core such that the surface area is more consistent from lot to lot to thereby improve the coating quality when the drug layer and the controlled release membrane layers are applied.

[0005] WO96/01621 refers to controlled release beads, optionally layered with a first inner layer of hydrophilic polymer, further layered with an active substance being optionally layered with an outer membrane for controlled release.

[0006] WO96/29992 discloses a controlled release diltiazem formulation comprising inert cores layered with the active substance and further layered with a polymeric coating material.

[0007] EP 0061 217 A2 describes an Ibuprofen containing sustained release pharmaceutical composition comprising spheroids consisting of a core and a layer of active principle applied on the core and an outer coating of active excipient forming the sustained release membrane.

[0008] According to the present invention, it has now surprisingly been found that by applying a relatively thick layer of a water-insoluble polymer to the inert core as a sealcoat, several advantages may be obtained in addition to those mentioned above.

[0009] Firstly, in case of a soluble core like one of sugar, for example, the amount of time that the solution within the bead would be saturated with respect to drug may be maximized. Thus, by preventing the soluble core from being a reservoir for drug dissolution, the relative time that a saturated solution would remain within the bead during the release period can be increased considerably. This means that a substantially longer zero order drug release phase (the phase when the drug release rate is essentially constant) will be obtained (and less in the undesirable declining release rate phase). In other words, generally, the use of a thick sealcoat layer will permit the drug release profile to be altered in a predictable fashion, in particular for drugs with a moderate to high water solubility. Also, without drug migrating into the sealcoat, all drug will get released.

[0010] Secondly, the potential influence of the core material on drug release, in particular osmotic pressure or swelling of the core material which could potentially cause internal pressure and film rupture, may be minimized.

[0011] Thirdly, the substantial initial lag phase (no or very low amount of drug release early) that is generally observed with the prior art controlled release beads, especially for slower release formulations where the water influx is slower, may be substantially reduced or eliminated relatively independently of the steady state release rate.

[0012] Therefore, in a first aspect, the present invention provides a controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material having;
(ii) a first layer on the core unit of a substantially water-insoluble polymer;
(iii) a second layer covering the first layer and containing an active ingredient; and
(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

[0013] The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

[0014] The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

[0015] Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

[0016] Usually, the first layer (ii) above constitutes more than 2% (w/w) of the final bead composition, preferably more than 3% (w/w), e.g. from 3% to 80% (w/w).

[0017] The amount of the second layer (ii) above usually constitutes from 0.05 to 60 % (w/w), preferably from 0.1 to 30 % (w/w) of the final bead composition.

[0018] The amount of the third layer (iv) above usually constitutes from 1 to 50 % (w/w), preferably from 2 to 25 % (w/w) of the final bead composition.

[0019] The core unit typically has a size in the range of from 0.05 to 2 mm.

[0020] In a second aspect, the present invention provides a multiple unit formulation comprising said controlled release beads, such as a capsule or a tablet.

[0021] The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. Especially, the beads are spheres of sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

[0022] The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (latex or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

[0023] The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

[0024] A wide variety of therapeutically active agents may be used in conjuction with the present invention. While the therapeutic agent usually is a low or medium dose drug, also high-dose drugs may be contemplated for use in the present invention. The therapeutic agent is preferably a soluble or moderately water-soluble drug (e.g. having a solubility corresponding to from less than 1 to about 30 ml of water per gram of solute at a temperature between 15 °C and 25 °C).

[0025] The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

[0026] Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

[0027] In a third aspect, the present invention provides a method for producing the controlled release beads and formulation, respectively. This method comprises the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;
b) applying a first layer of a substantially water-insoluble polymer to said core;
c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and
d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

[0028] Optionally, the method comprises the further step of applying one or more additional polymer layers to the core as has been mentioned above.

[0029] The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or

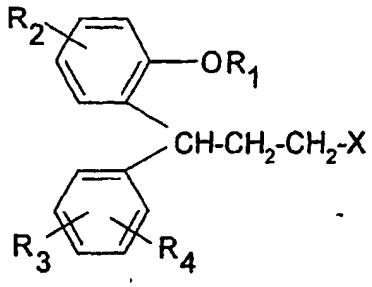
compressing the beads into tablets.

[0030] The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

[0031] After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

[0032] The pharmaceutical formulation of the invention may be administered orally.

[0033] An exemplary class of compounds which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. An exemplary specific compound is tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

[0034] Useful analogues to the above compounds are disclosed in WO 98/43942.

[0035] The above as well as the latter compounds have anti-cholinergic activity and may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The compounds also have spasmolytic activity and may be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

[0036] Specifically, the beads and multiple unit formulation, respectively, according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

[0037] Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urge incontinence, urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine. A salient feature of tolterodine is that it has considerably less side-effects than the previously conventionally used drug, oxybutynin, especially regarding the propensity to cause

dry mouth.

[0038] When tolterodine is the active ingredient in the controlled release bead, the fraction of active ingredient that is released in vitro is preferably not more than 30% after 1 hour, from 40 to 85% after 3 hours, and not less than 80% after 7 hours.

[0039] Administration of the controlled release formulation according to the present invention permits a well controlled release of tolterodine, and thereby a substantially constant serum level of active moiety or moieties to be maintained in the patient for at least 24 hours.

[0040] By the term "active moiety or moities" is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

[0041] The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, $AUC\tau$ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for $\underline{n}$ being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

[0042] For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

[0043] Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

[0044] Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e. g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

[0045] The invention will now be described in more detail by the following nonlimiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with different sealcoat thicknesses; and

Fig. 2 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with 14 % (w/w) and 0 % (w/w) seal coat, respectively. The polymer composition in the third layer of the beads with 0 % sealcoat has been adjusted in order to produce approximately similar initial drug release as from beads with 14 % sealcoat.

EXAMPLE 1

[0046] An exemplary bead containing tolterodine L-tartrate as active ingredient has the following structure:

Core: Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;

First layer: Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, con-

sisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;

Second layer: Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1;
purpose: drug supply;

Third layer: Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1; purpose: drug release rate control;

[0047] Beads with a three-layer coating having the above characteristics were prepared as follows:
[0048] 1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

[0049] After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

[0050] Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer : HPMC; comprises about 1 % w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

[0051] In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Study of effect of sealcoat thickness

[0052] The effect of the sealcoat thickness on drug release was tested as follows.
[0053] Four lots of 20-25 mesh beads were prepared that contained (i) a Surelease® sealcoat layer at 0, 2, 10 or 14% level, (ii) an HPMC/drug (tolterodine L-tartrate) layer at 4% level (drug:HPMC ratio =5:4), (iii) a Surelease®/HPMC layer at 10% level (Surelease®:HPMC ratio = 6:1 ratio), and (iv) a final HPMC layer at 1%. These were prepared essentially as described above and cured 1 hr at 70 °C.
[0054] Note that the coating level for layer (i) is expressed relative to the sum of the core plus sealcoat while coating levels for layers (ii-iv) are expressed relative to the final coated bead weight.
[0055] A fifth lot of beads was also manufactured identical to the 0% sealcoat lot described above except that the third coating layer was modified (increase in the Surelease®: HPMC layer from a 6:1 to a 11:1) such that the initial drug release rate was similar to the 14% sealcoat formulation described above.
[0056] The in vitro drug release at 37°C in phosphate buffer pH 6.8 with addition of 0.22M potassium chloride was measured. The USP dissolution test apparatus 1 was used. The results are shown in the diagrams in Fig. 1 and 2. As shown in Fig. 1, as the sealcoat layer gets thicker, the drug release rate both decreases and becomes more zero-order.
[0057] Fig. 2 shows the comparison of the 0% sealcoat formulation (11:1 Surelease®: HPMC) to the 14% sealcoat (6:1 the Surelease®: HPMC). It can be seen that, after a slight lag period observed by the 0% sealcoated beads, the

initial drug release rates are similar. However, after approximately 15-20% of the drug is released, the release rate from beads with 0 % sealcoat beads falls while release rate from the 14% sealcoat remains extremely zero order. Indeed, for the 0 % sealcoat beads the release rate between 45-60% is only approximately half of the initial (first 20 %) release rate. Comparatively, for the 14% sealcoat lot, the release rate between 45-60% range is identical to the rate over the first 20%.

[0058] In an analogous manner to the procedure described in Example 1 above, other exemplary bead formulations containing tolterodine L-tartrate as the active ingredient were prepared as described in Examples 2 and 3 below.

EXAMPLE 2

[0059] 400 g of sugar spheres (20-25 mesh, Edward Mendell Co, USA) were charged into a top-spray fluid bed coater (Nica, Sweden) and coated with Surelease® and thereafter cured in a drying cabinet at 70°C for 5 hours.

[0060] A solution of tolterodine-L-tartrate and hydroxypropyl cellulose (HPC) in water was sprayed onto the coated cores.

[0061] The spheres obtained were then coated with a mixture of ethylcellulose, hydroxypropylcellulose and triethyl-citrate (plasticizer). The coating materials were dissolved in a mixture of dichlormethane and ethanol.

[0062] The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	75.7
Surelease®	13
Tolterodine L-tartrate	4.9
HPC	1.5
Ethylcellulose	4.3
Triethyl citrate	0.6

[0063] The obtained spheres showed extended release of tolterodine L-tartrate over at least 10 hours. The release rate was essentially constant.

EXAMPLE 3

[0064] 4800 g of sugar spheres (18-20 mesh, Mendell, USA) were coated in a Wurster fluid bed with Surelease® to a theoretical weight gain of 10 % and thereafter cured in a drying cabinet at 60°C for 6 hours.

[0065] A solution of tolterodine L-tartrate and hydroxypropylmethyl cellulose (HPMC) in water was sprayed onto 1200 g of the cured sphere cores.

[0066] 1000 g of the obtained spheres were then coated by spraying with an aqueous dispersion of a cross-linked latex of hydroxyl-end blocked polydimethylsiloxan (PDMS, Dow Corning; USA) and colloidal silica (Dow Corning, USA) to a theoretical weight gain of 15%.

[0067] The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	76
Surelease®	7.8
Tolterodine L-tartrate	2.8
HPMC	0.4
PDMS	8.7
Colloidal silica	4.3

[0068] The obtained spheres showed extended release of tolterodine L-tartrate over at least 11 hours. The release rate was nearly constant.

Claims

1. A controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material;
(ii) a first layer on the core unit of a substantially water-insoluble polymer,

(iii) a second layer covering the first layer and containing an active ingredient; and
(iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

2. The bead according to claim 1, wherein the amount of polymer in said first layer is sufficient to substantially retard water penetration into the core.

3. The bead according to claim 1 or 2, wherein the thickness of said first layer is sufficient to affect the drug release rate from the bead.

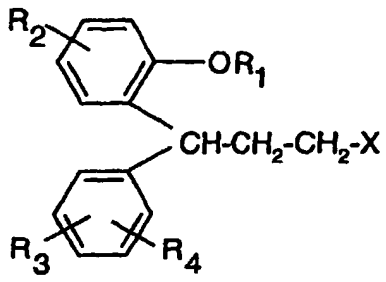
4. The bead according to claim 1, 2 or 3, wherein the amount of the first layer constitutes more than 2% (w/w), preferably more than 3% (w/w) of the final bead composition.

5. The bead according to any one of claims 1 to 4, wherein the amount of said second layer usually constitutes from 0.05 to 60 % (w/w), preferably from 0.1 to 30 % (w/w) of the final bead composition.

6. The bead according to any one of claims 1 to 5, wherein the amount of said third layer usually constitutes from 1 to 50 % (w/w), preferably from 2 to 25 % (w/w) of the final bead composition.

7. The bead according to any one of claims 1 to 6, wherein said third polymer layer is coated with a fourth layer of a water-soluble polymer or an additional functional coating.

8. The bead according to any one of claims 1 to 7, wherein said active ingredient is selected from compounds having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

9. The bead according to claim 8, wherein said active ingredient is selected from tolterodine, the 5-hydroxymethyl metabolite of tolterodine, the (S)-enantiomer of tolterodine, the 5-hydroxymethyl metabolite of the (S)-enantiomer of tolterodine, the racemate of tolterodine, and prodrug forms and pharmacologically acceptable salts thereof.

10. The bead according to claim 9, wherein said active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

11. The bead according to claim 10, wherein the fraction of active ingredient that is released in vitro is not more than

30% after 1 hour, from 40 to 85% after 3 hours, and not less than 80% after 7 hours.

12. The bead according to any one of claims 1 to 11, wherein the polymer material of said first layer comprises ethyl cellulose.

13. The bead according to any one of claims 1 to 12, wherein said second layer comprises hydroxypropylmethyl cellulose as binder.

14. The bead according to any one of claims 1 to 13, wherein the polymer material of said third layer comprises a combination of hydroxypropylmethyl cellulose and ethyl cellulose.

15. The bead according to any one of claims 1 to 14, wherein the core unit has a size of 0.05 to 2 mm.

16. A multiple unit formulation comprising a controlled release bead according to any one of claims 1 to 15.

17. The multiple unit formulation according to claim 16 which is a capsule.

18. A method of producing a controlled release bead, which method comprises the steps of:

a) providing a core unit of a substantially water-soluble or water-swellable material;
b) applying a first layer of a substantially water-insoluble polymer to said core;
c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and
d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first is selected to provide a layer thickness that permits control of water penetration into the core.

19. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating overactive bladder.

20. Use according to claim 19, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

21. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating nocturia.

22. Use according to claim 21, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

23. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating gastrointestinal disorders.

Patentansprüche

1. Perle mit gesteuerter Freisetzung, umfassend

i. eine Kerneinheit aus einem im wesentlichen wasser-löslichen oder in Wasser quellbaren inerten Material;
ii. eine erste Schicht aus einem im wesentlichen wasser-unlöslichen Polymer auf der Kemeinheit;
iii. eine zweite Schicht, die die erste Schicht bedeckt und einen Wirkstoff enthält, und
iv. eine dritte Schicht aus Polymer auf der zweiten Schicht, die wirksam ist zur gesteuerten Freisetzung des Wirkstoffs,

wobei die erste Schicht geeignet ist, das Eindringen von Wasser in den Kern zu steuern.

2. Perle nach Anspruch 1, wobei die Menge an Polymer in der ersten Schicht ausreichend ist, um das Eindringen von Wasser in den Kern wesentlich zu verzögern.

3. Perle nach Anspruch 1 oder 2, wobei die Dicke der ersten Schicht ausreichend ist, um die Freisetzungsgeschwindigkeit des Arzneimittels aus der Perle zu beeinflussen.

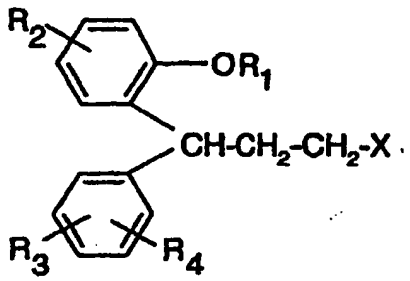
4. Perle nach Anspruch 1, 2 oder 3, wobei die Menge der ersten Schicht mehr als 2 Gew.%, vorzugsweise mehr als 3 Gew.%, der gesamten Perlenzusammensetzung ausmacht.

5. Perle nach einem der Ansprüche 1 bis 4, wobei die Menge der zweiten Schicht üblicherweise 0,05 bis 60 Gew.%, vorzugsweise 0,1 bis 30 Gew.%, der gesamten Perlenzusammensetzung ausmacht.

6. Perle nach einem der Ansprüche 1 bis 5, wobei die Menge der dritten Schicht üblicherweise 1 bis 50 Gew.%, vorzugsweise 2 bis 25 Gew.%, der gesamten Perlen-Zusammensetzung ausmacht.

7. Perle nach einem der Ansprüche 1 bis 6, wobei die dritte Polymerschicht mit einer vierten Schicht aus einem wasser-löslichen Polymer oder einem zusätzlichen funktionellen Überzug überzogen ist.

8. Perle nach einem der Ansprüche 1 bis 7, wobei der Wirkstoff ausgewählt ist aus Verbindungen der allgemeinen Formel



wobei R_1 Wasserstoff oder Methyl bedeutet, R_2, R_3 und R_4 unabhängig Wasserstoff, Methyl, Methoy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen bedeuten und X eine tertiäre Aminogruppe $-NR_5R_6$ bedeutet, wobei R_5 und R_6 nichtaromatische Kohlenwasserstoff-Gruppen, die gleich oder verschieden sein können, insbesondere C_1-C_6-Alkyl oder Adamantyl, bedeuten und die zusammen mindestens 3, vorzugsweise mindestens 4 Kohlenstoffatome enthalten, und von denen jede einen Hydroxy-Substituenten enthalten kann, und wobei R_5 und R_6 zusammen mit dem Amin-Stickstoff einen Ring, vorzugsweise einen nicht-aromatischen Ring, der kein Heteroatom außer dem Amin-Stickstoff enthält, bilden können, ihre Salze mit physiologisch annehmbaren Säuren und, wenn die Verbindungen in Form von optischen Isomeren vorliegen können, dem razemischen Gemisch und den einzelnen Enatiomeren.

9. Perle nach Anspruch 8, wobei der Wirkstoff ausgewählt ist aus Tolterodin, dem 5-Hydroxymethyl-Metaboliten von Tolterodin, dem (S)-Enantiomer von Tolterodin, dem 5-Hydroxymethyl-Metaboliten des (S)-Enantiomers von Tolterodin, dem Razemat von Tolterodin, und Vor-Arzneimittelformen und pharmakologisch annehmbaren Salzen davon.

10. Perle nach Anspruch 9, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

11. Perle nach Anspruch 10, wobei der Anteil an Wirkstoff, der in vitro freigesetzt wird, nach 1 Stunde nicht mehr als 30%, nach 3 Stunden 40 bis 85% und nach 7 Stunden nicht weniger als 80% beträgt.

12. Perle nach einem der Ansprüche 1 bis 11, wobei das Polymer-Material der ersten Schicht Ethylcellulose umfaßt.

13. Perle nach einem der Ansprüche 1 bis 12, wobei die zweite Schicht Hydroxypropylmethyl-celulose als Bindemittel umfaßt.

14. Perle nach einem der Ansprüche 1 bis 13, wobei das Polymer-Material der dritten Schicht eine Kombination von Hydroxypropylmethyl-celulose und Ethylcellulose umfaßt.

15. Perle nach einem der Ansprüche 1 bis 14, wobei die Kemeinheit eine Größe von 0,05 bis 2 mm hat.

16. Zubereitung mit mehreren Einheiten, umfassend eine Perle mit gesteuerter Freisetzung nach einem der Ansprüche 1 bis 15.

17. Zubereitung mit mehreren Einheiten nach Anspruch 16, die eine Kapsel ist.

18. Verfahren zur Herstellung einer Perle mit gesteuerter Freisetzung, wobei das Verfahren die folgenden Stufen umfaßt:

a) Bereitstellen einer Kerneinheit aus einem im wesentlichen wasser-löslichen oder in Wasser quellbaren Material;
b) Aufbringen einer ersten Schicht aus einem im wesentlichen wasser-unlöslichen Polymer auf den Kern;
c) Aufbringen einer zweiten Schicht, umfassend einen Wirkstoff und gegebenenfalls ein Polymer-Bindemittel, auf die erste Schicht und
d) Aufbringen einer dritten Polymer-Schicht, die wirksam ist zur gesteuerten Freisetzung des Wirkstoffs, auf die zweite Schicht,

wobei die Menge an Material in der ersten (Schicht) so ausgewählt wird, daß eine Schichtdicke entsteht, die es ermöglicht, das Eindringen von Wasser in den Kern zu steuern.

19. Verwendung einer therapeutisch wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung einer überaktiven Blase.

20. Verwendung nach Anspruch 19, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

21. Verwendung einer wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung von Nocturie.

22. Verwendung nach Anspruch 21, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

23. Verwendung einer therapeutisch wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung von gastrointestinalen Störungen.

Revendications

1. Perle à libération contrôlée comprenant :

(i) une unité noyau en un matériau inerte sensiblement hydrosoluble ou expansible dans l'eau ;
(ii) une première couche sur l'unité noyau en un polymère sensiblement insoluble dans l'eau ;
(iii) une deuxième couche couvrant la première couche et contenant un principe actif ; et
(iv) une troisième couche de polymère sur la deuxième couche efficace pour une libération contrôlée du principe actif,

dans laquelle ladite première couche est adaptée pour contrôler la pénétration de l'eau dans le noyau.

2. Perle selon la revendication 1, dans laquelle la quantité de polymère dans ladite première couche est suffisante pour retarder sensiblement la pénétration de l'eau dans le noyau.

3. Perle selon la revendication 1 ou 2, dans laquelle l'épaisseur de ladite première couche est suffisante pour affecter le taux de libération d'une substance médicamenteuse à partir de la perle.

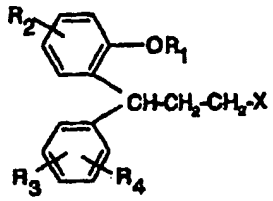
4. Perle selon la revendication 1, 2 ou 3, dans laquelle la quantité de la première couche représente plus de 2% (m/m), de préférence plus de 3% (m/m) de la composition finale de la perle.

5. Perle selon l'une quelconque des revendications 1 à 4, dans laquelle la quantité de ladite deuxième couche représente en règle générale de 0,05 à 60 % (m/m), de préférence de 0,1 à 30 % (m/m) de la composition finale de la perle.

6. Perle selon l'une quelconque des revendications 1 à 5, dans laquelle la quantité de ladite troisième couche représente en règle générale de 1 à 50 % (m/m), de préférence de 2 à 25 % (m/m) de la composition finale de la perle.

7. Perle selon l'une quelconque des revendications 1 à 6, dans laquelle ladite troisième couche de polymère est revêtue d'une quatrième couche d'un polymère hydrosoluble ou d'un revêtement fonctionnel additionnel.

8. Perle selon l'une quelconque des revendications 1 à 7, dans laquelle ledit principe actif est choisi parmi des composés ayant la formule générale suivante :



dans laquelle R_1 représente l'hydrogène ou le méthyle ; R_2, R_3 et R_4 sont de façon indépendante l'hydrogène, méthyle, métoxy, hydroxy, hydroxyméthyle, carbamoyl, sulphamoyl ou halogène; et X représente un groupe amino tertiaire - NR_5,R_6, dans lequel R_5 et R_6 sont des groupes hydrocarbyles non aromatiques, pouvant être identiques ou différents, en particulier un C_{1-6} -alkyle ou adamantyl, et contenant ensemble au moins trois, de préférence au moins quatre atomes de carbone, chacun d'entre eux pouvant porter un substituant hydroxy, et dans lequel R_5 et R_6 peuvent former un cycle conjointement avec l'azote de l'amine, de préférence un cycle non-aromatique n'ayant pas d'autre hétéroatome que l'azote de l'amine, leurs sels avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous la forme d'isomères optiques, le mélange racémique et les énantiomères individuels.

9. Perle selon la revendication 8, dans laquelle ledit principe actif est choisi parmi la toltérodine, le métabolite 5-hydroxyméthyle de la toltérodine, le (S)-énantiomère de la toltérodine, le métabolite 5-hydroxyméthyle du (S)-énantiomère de la toltérodine, le racémique de la toltérodine, ainsi que des formes de pro-médicaments et leurs sels pharmaceutiquement acceptables.

10. Perle selon la revendication 9, dans laquelle ledit principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

11. Perle selon la revendication 10, dans laquelle la fraction du principe actif qui est libérée in vitro ne dépasse pas 30 % après une heure, est de 40 à 85 % après trois heures, et n'est pas en-deçà de 80 % après sept heures.

12. Perle selon l'une quelconque des revendications 1 à 11, dans laquelle le matériau polymère de ladite première couche comprend l'éthylcellulose.

13. Perle selon l'une quelconque des revendications 1 à 12, dans laquelle ladite deuxième couche comprend l'hydroxypropylméthylcellulose en tant que liant.

14. Perle selon l'une quelconque des revendications 1 à 13, dans laquelle le matériau polymère de ladite troisième couche comprend une combinaison d'hydroxypropylméthylcellulose et d'éthylcellulose.

15. Perle selon l'une quelconque des revendications 1 à 14, dans laquelle l'unité noyau a une taille de 0,05 mm à 2 mm.

16. Formulation à unités multiples comprenant une perle à libération contrôlée selon l'une quelconque des revendications 1 à 15.

17. Formulation à unités multiples selon la revendication 16 sous forme d'une capsule.

18. Procédé de préparation d'une perle à libération contrôlée, ledit procédé comprenant les étapes suivantes :

a) fournir une unité noyau en un matériau sensiblement hydrosoluble ou expansible dans l'eau ;
b) appliquer une première couche d'un polymère sensiblement insoluble dans l'eau sur ledit noyau ;
c) appliquer sur ladite première couche une deuxième couche comprenant un principe actif et éventuellement un liant polymère ; et
d) appliquer sur ladite deuxième couche une troisième couche polymère efficace pour une libération contrôlée du principe actif ;

dans lequel la quantité de matériau dans ladite première couche est choisie de façon à fournir une épaisseur de couche permettant de contrôler la pénétration de l'eau dans le noyau.

19. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement de l'hyperactivité de la vessie.

20. Utilisation selon la revendication 19, dans lequel le principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

21. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement de la nocturie.

22. Utilisation selon la revendication 21, dans laquelle le principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

23. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement des troubles gastro-intestinaux.

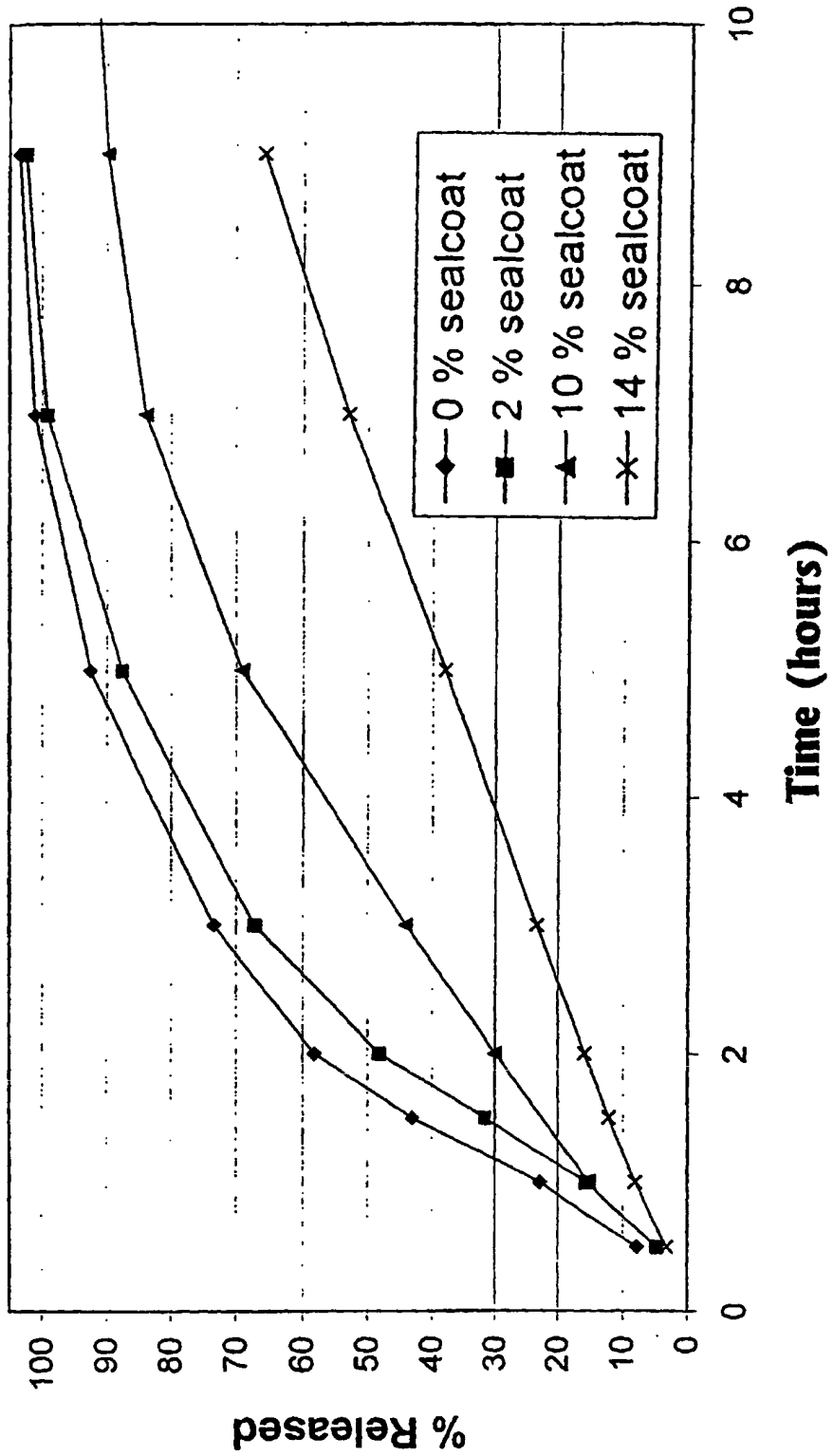


FIG. 1

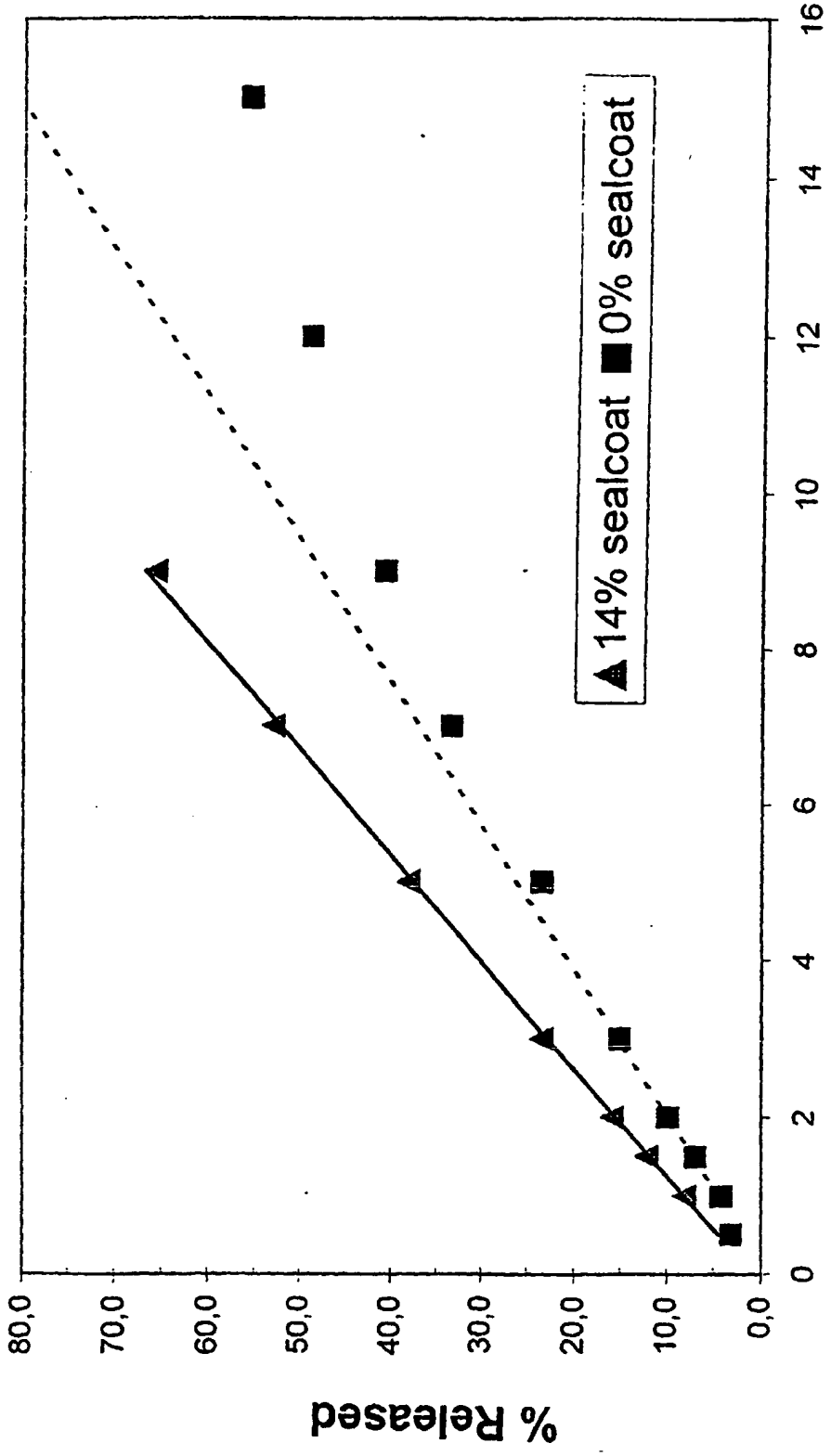


FIG. 2

1,169,944

PATENT SPECIFICATION

NO DRAWINGS

1,169,944

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38195/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance:—C2 C(1H1A3, 1H1C2, 1Q2, 1Q3, 1Q6B1, 1Q7A, 1Q8A, 1Q8C, 1Q9C, 1Q9F2, 1Q11D, 1Q11J, 2A2, 2A5, 2A14, 2R17, 22Y, 220, 226, 227, 29Y, 29X, 30Y, 304, 32Y, 323, 36Y, 364, 650, 662, 682, 790, LF)

International Classification:—C 07 c 87/28, 93/14

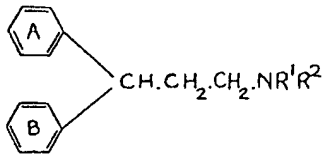
COMPLETE SPECIFICATION

Novel 3,3-Diphenylpropylamines and processes for the preparation thereof

We, ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate organised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new 3,3-diphenylpropylamine derivatives which have antidepressant activity.

According to the invention we provide alkane derivatives of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, and R^2 stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, and acid-addition salts thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R^1 and R^2 do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R^1 and R^2 do not both stand for the ethyl radical.

As a suitable value for R^2, or for R^1 when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl radical.

The substituent(s) which may be present in the phenyl radical A may, for example, be selected from fluorine and chlorine atoms, and the trifluoromethyl radical. The substituent(s) which is or are present in the phenyl radical (B) may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms, for example the methyl and methoxy radical.

Preferred compounds of the invention are those wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

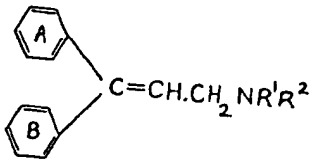
As specific alkane derivatives of the invention there may be mentioned, by way of example, N,N - dimethyl - 3, 3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl)-3-phenylpropylamine, N,N - dimethyl - 3,3 - bis-(4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - fluorophenyl)propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)-propylamine, N,N - dimethyl - 3,3 - bis - (3-trifluoromethylphenyl)propylamine and N,N -

[Price 4s. 6d.]

dimethyl - 3 - (3 - trifluoromethylphenyl)-3 - phenylpropylamine, and acid-addition salts thereof.

As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

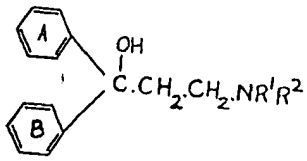
According to a further feature of the invention we provide a process for the manufacture of the alkane derivatives of the invention, which comprises reducing an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof.

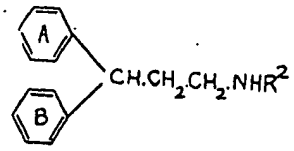
The reduction may be carried out, for example, by catalytic hydrogenation, for example by hydrogenation in the presence of a palladium-on-carbon catalyst. The hydrogenation may be carried out in an inert diluent or solvent, for example ethanol, and it may be carried out at ambient temperature or under the influence of heat, and at atmospheric or an elevated pressure. Alternatively, for example, the reduction may be carried out by the interaction of the alkene derivative with red phosphorus and hydriodic acid. In this case the alkene derivative may conveniently be formed *in situ* by interaction of the corresponding tertiary alcohol with red phosphorus and hydriodic acid.

The alkene derivatives used as starting materials in the above process (some of which are described and claimed in our co-pending Application No. 8165/66 (Serial No. 1134715) may be obtained by dehydrating the corresponding hydroxy compounds of the formula:

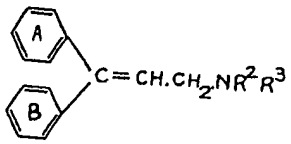


wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof, by the interaction thereof with hydrochloric acid in the presence of a diluent or solvent, for example acetic acid.

According to a further feature of the invention we provide a process for the manufacture of those of the alkane derivatives of the invention which are of the formula:—



wherein A, B and R^2 have the meanings stated above, and acid-addition salts thereof, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R^2 have the meanings stated above, and R^3 stands for a hydrogenolysable group, or an acid-addition salt thereof.

As a suitable value for R^3 there may be mentioned, for example, the benzyl radical. The hydrogenolysis may be carried out by catalytic hydrogenation using the reactants and conditions described above.

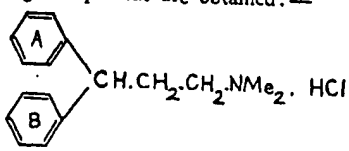
The starting materials in the last-named process may be obtained by the general dehydration process outlined above.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

5 Parts of N,N - dimethyl - 3,3 - bis - (4-fluorophenyl)prop- 2 -enylamine hydrochloride are dissolved in 20 parts of dry ethanol. 2.5 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated to a small volume. Dry ether is slowly added until crystallisation begins, and 500 parts of dry ether are then added. The mixture is filtered and the solid residue is washed with dry ether and then dried. The solid is crystallised from ethyl acetate containing a trace of ethanol, and there is thus obtained N,N-dimethyl-3,3 - bis - (4 - fluorophenyl)propylamine hydrochloride, m.p. 188—189°C.

In a similar manner, using the appropriate alkene derivative as starting material, the following compounds are obtained:—



A	B	m.p. (°C.)	Crystallisation solvent(s)
Ph	4—F—Ph	141—144	n-butyl acetate
Ph	4—Cl—Ph	154—157	ethyl acetate—trace of ethanol
Ph	3—F—Ph	166—168	"
Ph	2—Me—Ph	165—167	"
Ph	2—MeO—Ph	166—167	"
Ph	3—CF_3—Ph	145—148	ethyl acetate — petroleum ether (b.p. 60—80°C.)
4—Cl—Ph	4—Cl—Ph	193—196	n-butyl acetate
4—Cl—Ph	4—F—Ph	173—176	n-butyl acetate
3—F—Ph	3—F—Ph	178—180	ethyl acetate—trace of ethanol
3—CF_3—Ph	3—CF_3—Ph	158—160	ethyl acetate — petroleum ether (b.p. 60—80°C.)

The N,N - dimethyl - 3,3 - bis-(4-fluorophenyl)prop - 2 - enylamine hydrochloride used as starting material in the process described above may be obtained as follows:—

A mixture of 6 parts of N,N - dimethyl-3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine (m.p. 120°C.), 50 parts of acetic acid and 15 parts of 10N-hydrochloric acid is heated at 100°C. for 3 hours. The reaction mixture is evaporated to small volume and the residual oil is dissolved in water. The solution is washed with ether and is then made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and an ethereal solution of hydrogen chloride is then added to the extract until the precipitation of solid is complete. The precipitated solid is collected by filtration and is then crystallised from butyl acetate. There is thus obtained N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, m.p. 209°C.

The N, N - dimethyl - 3,3 - bis - (4-fluorophenyl) - 3 - hydroxypropylamine used as starting material can be obtained in conventional manner by the interaction of the appropriate Grignard reagent with the appropriate ketone.

The alkene derivatives used as starting materials for the preparation of the alkane derivatives listed in the above table may be obtained in similar manner to that described for N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)prop - 2 - enylamine hydrochloride.

EXAMPLE 2

6 Parts of N - benzyl - N - methyl-3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride are dissolved in 30 parts of dry ethanol. 3 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated. The residue is dissolved in 50 parts of water, and the solution is basified with ammonia. The base is extracted twice, each time with 100 parts of ether, and the combined ethereal extracts are dried with anhydrous magnesium sulphate. To the dry ethereal solution there is added an ethereal solution of oxalic acid until precipitation is complete. The mixture is filtered, and the solid residue is washed with ether and then dried on the filter. The solid is crystallised from ethanol, and there is thus obtained N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine oxalate, m.p. 187—190°C.

The N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride used as starting material may be obtained as follows:—

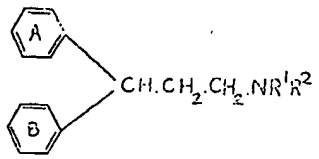
A mixture of 58.3 parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine, 465 parts of acetic acid and 117 parts of 10N-hydrochloric acid is heated under reflux for 0.5 hour. The mixture is evaporated to small volume and the residual oil is dissolved in water. The solution

is made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and is evaporated *in vacuo*. The residual oil is fractionally distilled at a pressure of 0.2mm. Hg. and the fraction having b.p. 172—178°C. is collected. There is thus obtained N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, which may be converted into the hydrochloride (m.p. 132°C.) by conventional means.

N - Benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine can be obtained in conventional manner by the interaction of ethyl 3 - (N - benzyl - N - methylamino)propionic acid and the appropriate Grignard reagent.

WHAT WE CLAIM IS:—

1. An alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, and R^2 stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R^1 and R^2 do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R^1 and R^2 do not both stand for the ethyl radical.

2. A compound as claimed in claim 1 wherein R^1 stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R^2 stands for an alkyl radical of not more than 6 carbon atoms, and the phenyl radical A optionally bears one or two substituents selected from fluorine and chlorine atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

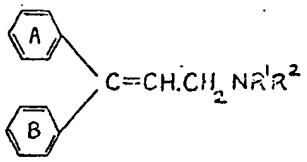
3. A compound as claimed in claim 1 wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

4. A compound as claimed in claim 3 wherein the halogen substituent(s) present in phenyl radical B, and optionally present in phenyl radical A, is or are selected from fluorine and chlorine atoms.

5. A compound selected from N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3,3 - bis - (4 - chlorophenyl)-propylamine, N,N - dimethyl - 3 - (4-chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3-fluorophenyl)-propylamine, N - methyl - 3,3 - bis - (4-fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

6. An acid-addition salt as claimed in any of claims 1 to 5 which is a hydrochloride, oxalate, citrate, maleate or tartrate.

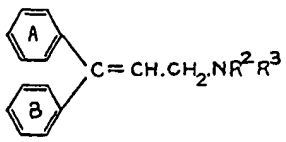
7. A process for the manufacture of a compound claimed in any of claims 1 to 6, which comprises reducing an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated in claim 1, or an acid-addition salt thereof.

8. A process as claimed in claim 7 in which the reduction is carried out by hydrogenation in the presence of a palladium-on-carbon catalyst.

9. A process for the manufacture of a compound claimed in claim 1 wherein R^1 stands for hydrogen, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R^2 have the meanings stated above, and R^3 stands for a hydro-

genolysable group, or an acid-addition salt thereof.

10. An alkane derivative, claimed in claim 1, substantially as described in either of the foregoing Examples.

11. A process for the manufacture of an alkane derivative, claimed in claim 7 or 9, substantially as described in either of the foregoing Examples.

B. F. DREW,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

1,169,945

PATENT SPECIFICATION

NO DRAWINGS

1,169,945

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38196/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance:—A5 B(38Y, 383, 43Y, 431, 58Y, 586, 64Y, 641)

International Classification:—A 61 k 27/00

COMPLETE SPECIFICATION

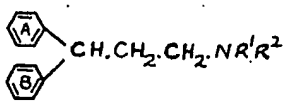
Pharmaceutical Compositions containing Diphenylalkylamine Derivatives

We, ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate oganised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pharmaceutical compositions having antidepressant activity.

Certain 3,3-diphenylpropylamine derivatives are known compounds, but it was not known heretofore that compounds of this type were useful as antidepressants. We have now made the unexpected discovery that compounds of this type have antidepressant activity, and therein lies the basis of this invention.

According to the invention we provide pharmaceutical compositions comprising at least one alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, R^2 stands for an alkyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

As a suitable value for R^1, or for R^1 when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl or ethyl radical.

The substituent(s) which may optionally be present in either or both or the phenyl radicals A and B may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkoxy and alkyl radicals of not more than 3 carbon atoms, for example the methoxy or methyl radical.

A preferred group of active ingredients consists of alkane derivatives of the above formula wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

As alkane derivatives which may be used as active ingredients in the pharmaceutical compositions of the invention there may be mentioned, for example, the known compounds N,N - dimethyl - 3,3 - diphenylpropylamine, N - methyl - 3,3 - diphenylpropylamine, and N - ethyl - N - methyl - 3,3 - diphenylpropylamine, and the new compounds: N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - fluorophenyl)propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

[*Price 4s. 6d.*]

As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

Suitable pharmaceutically-acceptable diluents or carriers for use as excipients in the compositions of the invention are those known to the art and used in the preparation of pharmaceutical formulations for human and veterinary medication.

The pharmaceutical compositions of the invention include compositions which are suitable for oral administration. These include, for example, solid compositions, for example tablets, pills, capsules, dispersible powders and granules, which may optionally be coated, for example with a sweetening agent and/or a protective material designed to modify the distribution and absorption of the active ingredient or ingredients in the digestive tract. They also include orally-administerable semi-solid or liquid formations, for example pharmaceutically-acceptable emulsions, syrups, dispersions and solutions, either for administration *per se* with or without flavouring agents or after confinement in some suitable way, for example in capsules.

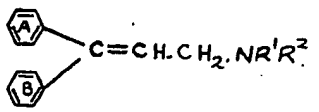
The pharmaceutical compositions of the invention also include liquid compositions which are sterile aqueous solutions, suspensions or emulsions, or sterile non-aqueous solutions or suspensions which can be administered by injection, for example intravenously, subcutaneously or intramuscularly. Those injectable compositions of the invention which are suspensions contain their particulate matter in a finely divided form, for example in a micro-pulverised form, and those compositions which are aqueous suspensions may optionally contain small amounts of such agents as are commonly used to facilitate the manufacture and maintain the efficacy of aqueous suspensions, for example dispersing and suspending agents.

Suitable vehicles for the non-aqueous solutions and suspensions of the invention include, for example, water-miscible non-toxic vehicles, for example propylene glycol and polyethylene glycol, and water-immiscible non-toxic vehicles, for example injectable vegetable oils, for example arachis oil, and oil-like injectable organic esters, for example dibutyl succinate. The said water-immiscible vehicles may also contain metallic soaps, for example aluminium stearate.

The sterile injectable solutions, suspensions or emulsions of the invention may be obtained sterile by known precedures, for example by aseptic formulation, by Seitz filtration, by irradiation, by the incorporation of sterilising agents in the compositions, or by heat treatment.

The compositions of the invention include pharmaceutical compositions which are sterile powders comprising the active ingredient or ingredients together with such non-toxic pharmaceutical excipients as are required to provide, on mixing with water, sterile aqueous solutions or suspensions suitable for parenteral administration.

The alkane derivatives which are used as the active ingredients in the pharmaceutical compositions of this invention may be obtained by the reduction of an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof, as described in our co-pending patent application No. 38195/66 (Serial No. 1,169,944) of even date herewith, or by analogous means.

The invention is illustrated but not limited by the following Example in which the parts are by weight:—

EXAMPLE

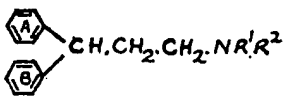
A mixture of 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride, 125 parts of maize starch, 270 parts of calcium phosphate and 1 part of magnesium stearate is compressed, and the compressed material is then broken down into granules by passage through a 16-mesh screen. The granules so obtained are then compressed into tablets which are suitable for oral administration for therapeutic purposes.

In place of the 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride used in the above example there may be used 25 parts of any of the following compounds:—

N - methyl - 3,3 - diphenylpropylamine hydrocloride, N - ethyl - 3,3 - diphenylpropylamine hydrochloride or N - ethyl - N-methyl - 3,3 - diphenylpropylamine hydrochloride. It is to be understood that the pharmaceutical compositions claimed in the following claims do not include simple solutions of the alkane derivatives(s) in question in common solvents for example water.

Subject to this disclaimer, WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising at least one alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, R^2 stands for an alkyl radical, and either or both of the phenyl radicals A and B

may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

2. A composition as claimed in claim 1 wherein R^1 stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R^2 stands for an alkyl radical of not more than 6 carbon atoms, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radicals, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

3. A composition as claimed in claim 1 wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

4. A composition as claimed in claim 3 wherein the halogen substituent(s) is or are selected from fluorine and chlorine atoms.

5. A composition as claimed in claim 1 in which the active ingredient is N,N - dimethyl-3,3 - diphenylpropylamine or an acid-addition salt thereof.

6. A composition as claimed in claim 1 in which the active ingredient(s) is or are selected from N - methyl - 3,3 - diphenylpropylamine, N - ethyl - N - methyl - 3,3 - diphenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4-fluorophenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3,3 - bis - (4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - fluorophenyl) propylamine, N - methyl - 3,3 - bis - (4-fluorophenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

7. A composition as claimed in any of claims 1 to 6 which is in the form of a tablet, pill, capsule, dispersible powder or granule, emulsion, syrup, dispersion, non-sterile solution, or a sterile injectable aqueous solution, suspension or emulsion or a sterile injectable non-aqueous solution or suspension, or a sterile powder.

8. A tablet, claimed in claim 7, substantially as described in the foregoing Example.

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Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 93/23025
A61K 31/135, 9/70, 47/14	A1	(43) International Publication Date: 25 November 1993 (25.11.93)

(21) International Application Number: PCT/US93/04518

(22) International Filing Date: 13 May 1993 (13.05.93)

(30) Priority data:
882,652 13 May 1992 (13.05.92) US

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(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: TRANSDERMAL ADMINISTRATION OF OXYBUTYNIN

(57) Abstract

The present invention is directed to the transdermal administration of oxybutynin together with a suitable permeation enhancer. The invention includes a transdermal drug delivery device comprising a matrix adapted to be placed in oxybutynin- and permeation enhancer-transmitting relation with the skin site. The matrix contains sufficient amounts of a permeation enhancer and of oxybutynin, in combination, to continuously administer to the skin for a predetermined period of time the oxybutynin to provide an effective therapeutic result. The invention is also directed to a method for the transdermal administration of a therapeutically effective amount of oxybutynin together with a skin permeation-enhancing amount of a suitable permeation enhancer.

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TRANSDERMAL ADMINISTRATION OF OXYBUTYNIN

FIELD OF THE INVENTION

This invention relates the efficacious and safe, controlled transdermal administration of oxybutynin and related compounds for the treatment of neurogenic bladder disorders.

BACKGROUND OF THE INVENTION

Neurogenic bladder disease is a disorder involving loss of control of urination. The major symptoms of this disease are urinary frequency, urinary retention or incontinence. There are two types of lesions that cause a neurogenic bladder. The first, upper motoneuron lesion, leads to hypertonia and hyperreflexia of the bladder, a spastic condition, giving rise to symptoms of urinary frequency and incontinence. The second lesion, a lower motoneuron lesion, involves hypotonia and hyporeflexia of the bladder. The major symptoms in this condition are urinary retention, since the voiding reflex has been lost, and incontinence, which occurs when the bladder "leaks", being full to overflowing.

The majority of neurogenic bladder patients have the spastic or hypertonic bladder. The clinician usually attempts to convert the condition of hyperreflexia and hypertonia to hypotonia, thereby treating the primary problem of incontinence. When the condition has been converted to hypotonia, it can be managed by intermittent catheterization. However, there is a significant population of patients who cannot be converted completely from the hypertonic to the hypotonic condition, and who still find they have to urinate every hour or are incontinent. For these patients, treatment with an anticholinergic drug is necessary. The drug of choice is oxybutynin (4-diethylamino-2-butynylphenylcyclohexylglycolate).

The use of oxybutynin chloride, as approved by the FDA in the United States, is described in the 1992 Physician's Desk Reference, pages 1332 through 1333 with reference to the drug Ditropan® manufactured by Marion Merrell Dow. Oxybutynin is normally administered to human beings orally at relatively high doses (5 mg

tablets taken two to four times a day). Oxybutynin has been incorporated into tablets, capsules, granules or pills containing 1-5 mg, preferably 5 mg, of oxybutynin chloride, syrups containing 1-5 mg, preferably 5 mg, of oxybutynin chloride per 5 ml and transdermal compositions (creams or ointments) containing 1-10 weight percent ("wt %") oxybutynin chloride. See, BE 902605.

In U.S. Patent No. 4,747,845, oxybutynin was listed as an agent that could be incorporated into a transdermal synthetic resin matrix system for extended duration drug release, but oxybutynin was not used in the device. In U.S. Patent No. 4,928,680 oxybutynin was given as a pharmacologically active agent suitable for transdermal delivery, but as with the above reference, oxybutynin was not incorporated into the device.

Oxybutynin has been incorporated into a device having a water impermeable barrier layer, a reservoir containing oxybutynin in contact with the inner surface of the barrier layer and a removable protector layer in contact with the other surface of the reservoir. The reservoir is a polyurethane fiber mat impregnated with an aqueous solution containing 25 mg/ml of oxybutynin. The device was placed on a 20 μm thick polybutadiene film. The non-device carrying surface was in contact with 0.05 M isotonic phosphate buffer solution. The *in vitro* release rate measured was approximately 12 mg over 24 hours through a 49 cm^2 area or 10 $\mu g/cm^2/hr$. (U.S. Patent No. 4,784,857 and EP 0 250 125).

In Pharm Res, "Development of Transdermal Delivery Systems of Oxybutynin: In-Vivo Bioavailability", P. Keshary *et al.*, (NY)8 (10 Supp) 1991, p. S205 three types of transdermal delivery systems, using matrix-diffusion controlled and membrane-permeation controlled technologies were discussed. The *in vitro* permeation rate of about 9, 12 and 12 $\mu g/cm^2/hr$ and *in vitro* release rates (sink condition) of about 1160, 402 and 57.2 $\mu g/cm^2/hr$ were obtained from Silastic monolithic, acrylic pressure sensitive adhesive matrix and reservoir type delivery systems, respectively. In humans, steady state plasma concentrations of about 1.86 ng/ml were obtained after 6 hours of

application of a single 20 cm^2 patch of the acrylic pressure sensitive adhesive matrix type.

The transdermal route of administration for drugs and other biologically active agents ("agents") has been proposed for a wide variety of systemically acting and locally acting agents on either a rate-controlled or non rate-controlled basis and is described in numerous technical publications and patents, such as U.S. Patents 3,598,122; 3,598,123; 3,731,683; 3,797,494; 4,031,894; 4,201,211; 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,588,580; 4,645,502; 4,704,282; 4,788,062; 4,816,258; 4,908,027; 4,943,435; and 5,004,610. The disclosures of the above patents are incorporated herein by reference.

Just as certain drugs can irritate, sensitize or be otherwise toxic, so can permeation enhancers. The use of permeation enhancers for transdermal administration is described in numerous technical publications and patents, such as U.S. Patents Nos. 4,940,586; 4,863,738; 4,820,720; 4,746,515; 4,568,343; 4,405,616; 4,379,454; 4,343,798; 4,335,115; 4,299,826; 4,130,667; 4,130,643; 4,046,886; British Patent No. 1,001,949 and Idson, Percutaneous Absorption, J. Phar. Sci., Vol. 64, No. 66, June 1975, pp. 901-924.

Permeation enhancers that are not normally toxic at the concentrations employed in cosmetic or medical compositions may exhibit toxic effects at the higher concentrations required to produce adequate permeation enhancement. No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.

Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many

potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.

The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system.

As used herein, the term "oxybutynin" is used to designate oxybutynin, acid addition salts of oxybutynin and the related compounds thereof. The preferred active agent according to the present invention is oxybutynin itself. Oxybutynin is a base capable of forming acid addition salts with organic and mineral acids, for example, with hydrochloric acid to form oxybutynin chloride. Preferably, the device of this invention contains oxybutynin as the free base.

As used herein, the term "transdermal" delivery or application refers to the delivery or application of oxybutynin by passage through skin, mucosa and/or other body surfaces by topical application.

As used herein, the term "therapeutically effective" amount or rate refers to the amount or rate of oxybutynin needed to effect the desired therapeutic result.

As used herein, the term "monoesters" refers to those monoesters having from 10 to 20 carbon atoms.

As used herein, the term "glycerol monooleate" refers to glycerol monooleate itself or a mixture of monoglycerides wherein glycerol monooleate is present in the greatest amount.

As used herein, the term "glycerol monolaurate" refers to glycerol monolaurate itself or a mixture of monoglycerides wherein glycerol monolaurate is present in the greatest amount.

As used herein, the term "glycerol monolinoleate" refers to glycerol monolinoleate itself or a mixture of monoglycerides wherein glycerol monolinoleate is present in the greatest amount.

The above summarizes the primary characteristics recognized to date that affect suitability of oxybutynin and a permeation enhancer for transdermal administration. There are undoubtedly others, some of which have not yet been recognized. In order for oxybutynin and a permeation enhancer to be suitable for transdermal administration they must possess the right combination of all of these characteristics, a combination which is quite rare and unpredictable.

SUMMARY OF THE INVENTION

According to the present invention, it has been discovered that oxybutynin may be safely and efficaciously administered transdermally, together with a suitable permeation enhancer, preferably a monoglyceride or mixture of monoglycerides of fatty acids with a total monoester content of at least 51%. The invention includes a transdermal drug delivery device containing sufficient amounts of permeation enhancer and of oxybutynin, in combination, to provide systemic administration of oxybutynin through the skin for a predetermined period of time for the oxybutynin to provide an effective therapeutic result.

The invention is also directed to a method for the transdermal administration of a therapeutically effective amount of oxybutynin together with a skin permeation-enhancing amount of a suitable permeation enhancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-section through a schematic perspective view of one embodiment of transdermal therapeutic devices according to this invention.

FIG. 2 is a cross-section through another embodiment of a transdermal therapeutic device according to this invention.

FIG. 3 is a cross-section through another embodiment of a transdermal therapeutic device according to this invention.

FIG. 4 is a cross-section through yet another embodiment of a transdermal therapeutic device according to this invention.

FIG. 5 shows the oxybutynin permeation rate through the epidermis at 35°C with various permeation enhancers.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

According to the present invention, it has been found that oxybutynin may be administered to the human body in a therapeutically effective amount via the transdermal route when it is co-administered with a suitable permeation enhancer. Therapeutic blood levels from about 0.5 ng/ml to about 3.0 ng/ml can be obtained from administration rates in the range of 0.08 mg/hr to 0.5 mg/hr. Representative skin permeation rates of oxybutynin through living human skin are in the range of about 12 $\mu g/cm^2/hr$ to about 40 $\mu g/cm^2/hr$, depending on the permeation enhancer. Therapeutic blood levels can be achieved within approximately 1-5 hours, and peak blood concentrations are achieved at about 3 hours when the system is worn for 24 hours. The range of desired and achievable system permeation rates of oxybutynin, arriving through the skin from a limited area, is 1-20 mg over a period of 24 hours. The system application is easily adapted for shorter or longer duration treatments, but generally 24 hours is the nominal duration for treatment.

Typical transdermal delivery devices are described in U.S. patent numbers 3,598,122; 3,598,123; 4,286,592; 4,314,557; 4,379,454; 4,559,222; 4,573,995; and 4,849,226, for example. All of these are incorporated herein by reference. The co-administration of

oxybutynin and a permeation enhancer as disclosed herein can be accomplished by using transdermal devices of these kinds.

Because of the wide variation in skin permeability from individual and from site to site on the same body, it may be preferable that oxybutynin and the permeation enhancer be administered from a rate-controlled transdermal delivery device. Rate control can be obtained either through a rate-controlling membrane or adhesive or through the other means disclosed in the patents noted above.

A certain amount of oxybutynin will bind to the skin, and it is accordingly preferred that the skin-contacting layer of the device include this amount of the agent as a loading dose.

Examples of suitable transdermal delivery devices are illustrated in FIGS. 1, 2 and 3. In the drawings, the same reference numbers are used throughout the different figures to designate the same or similar components. The figures are not drawn to scale.

In FIG. 1, transdermal delivery device 10 comprises a reservoir 12 containing both oxybutynin and a suitable permeation enhancer. Reservoir 12 is preferably in the form of a matrix containing oxybutynin and enhancer dispersed therein. Reservoir 12 is sandwiched between a backing layer 14, which is permeable to water vapor, and an in-line contact adhesive layer 16. Preferably, the backing is a spun-laced polyester, such as Sontara®, a nylon reinforced polyurethane, such as NRU-100-C Flexcon® or a multilaminate film layer, such as EVA/EVA/polyvinyldienefluoride /EVA/EVA film layer Saranex® Type 52. The device 10 adheres to the surface of the skin 18 by means of the adhesive layer 16. The adhesive layer 16 may optionally contain enhancer and/or oxybutynin. A strippable release liner (not shown in FIG. 1) is normally provided along the exposed surface of adhesive layer 16 and is removed prior to application of device 10 to the skin 18. Optionally, a rate-controlling membrane (not shown) may be present between the reservoir 12 and the adhesive layer 16.

Alternatively, as shown in FIG. 2, transdermal therapeutic device 20 may be attached to the skin or mucosa of a patient by means

of an adhesive overlay 22. Device 20 is comprised of a oxybutynin- and permeation enhancer-containing reservoir 12 which is preferably in the form of a matrix containing oxybutynin and the enhancer dispersed therein. A backing layer 14, which is impermeable to oxybutynin, the permeation enhancer and water vapor, is provided adjacent one surface of reservoir 12. Adhesive overlay 22 maintains the device on the skin and may be fabricated together with, or provided separately from, the remaining elements of the device. With certain formulations, the adhesive overlay 22 may be preferable to the in-line contact adhesive 16 as shown in FIG. 1. This is true, for example, where the oxybutynin/enhancer reservoir contains a material which adversely affects the adhesive properties of the in-line contact adhesive layer 16. Backing layer 14 is preferably slightly larger than reservoir 12, and in this manner prevents the materials in reservoir 12 from adversely interacting with the adhesive in overlay 22. Optionally, a rate-controlling membrane (not shown in FIG. 2) may be provided on the skin-proximal side of reservoir 12. A strippable release liner 24 is also provided with device 20 and is removed just prior to application of device 20 to the skin.

In FIG. 3, transdermal delivery device 30 comprises a oxybutynin and permeation enhancer containing reservoir ("oxybutynin reservoir") 12 substantially as described with respect to FIG. 1. Permeation enhancer reservoir ("enhancer reservoir") 26 comprises permeation enhancer dispersed throughout and is substantially free of any undissolved oxybutynin. Enhancer reservoir 26 is preferably made from substantially the same matrix as is used to form oxybutynin reservoir 12. A rate-controlling membrane 28 for controlling the release rate of the permeation enhancer from enhancer reservoir 26 to oxybutynin reservoir 12 is placed between the two reservoirs. A rate-controlling membrane (not shown in FIG. 3) for controlling the release rate of the enhancer from oxybutynin reservoir 12 to the skin may also optionally be utilized and would be present between adhesive layer 16 and reservoir 12.

The rate-controlling membrane may be fabricated from permeable, semipermeable or microporous materials which are known in the art to control the rate of agents into and out of delivery devices and having a permeability to the permeation enhancer lower than that of oxybutynin reservoir 12. Suitable materials include, but are not limited to, polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers.

Superimposed over the permeation enhancer reservoir 26 of device 30 is a backing 14 that is permeable to water vapor. On the skin-proximal side of reservoir 12 are an adhesive layer 16 and a strippable liner 24 which would be removed prior to application of the device 30 to the skin.

In the embodiments of FIGS. 1, 2 and 3, the carrier or matrix material of the reservoirs has sufficient viscosity to maintain its shape without oozing or flowing. If, however, the matrix or carrier is a low viscosity flowable material such as a liquid or a gel, the composition can be fully enclosed in a pouch or pocket, as known to the art from U.S. Pat. No. 4,379,454 (noted above), for example, and as illustrated in FIG. 4.

Device 40 shown in FIG. 4 comprises a backing member 14 which serves as a protective cover for the device, imparts structural support, and substantially keeps components in device 40 from escaping the device. Device 40 also includes reservoir 12 which contains the oxybutynin and permeation enhancer and bears on its surface distant from backing member 14 a rate-controlling membrane 28 for controlling the release of oxybutynin and/or permeation enhancer from device 40. The outer edges of backing member 14 overlay the edges of reservoir 12 and are joined along the perimeter with the outer edges of the rate-controlling membrane 28 in a fluid-tight arrangement. This sealed reservoir may be effected by pressure, fusion, adhesion, an adhesive applied to the edges, or other methods known in the art. In this manner, reservoir 12 is contained wholly between backing member 14 and rate-controlling membrane 28. On the skin-proximal side of rate-controlling membrane 28 are an adhesive

layer 16 and a strippable liner 24 which would be removed prior to application of the device 40 to the skin.

In an alternative embodiment of device 40 of FIG. 4, reservoir 12 contains the permeation enhancer only and is substantially free of oxybutynin. The oxybutynin and an additional amount of permeation enhancer are present in adhesive layer 16 which acts as a separate reservoir.

The oxybutynin and the permeation enhancer can be co-extensively administered to human skin or mucosa by direct application to the skin or mucosa in the form of an ointment, gel, cream or lotion, for example, but are preferably administered from a skin patch or other known transdermal delivery device which contains a saturated or unsaturated formulation of oxybutynin and the enhancer.

The formulation may be aqueous or non-aqueous based. The formulation should be designed to deliver the oxybutynin and the permeation enhancer at the necessary release rates. Aqueous formulations typically comprise water or water/ethanol and about 1-2 wt % of a gelling agent, an example being a hydrophilic polymer such as hydroxyethylcellulose or hydroxypropylcellulose. Typical non-aqueous gels are comprised of silicone fluid or mineral oil. Mineral oil-based gels also typically contain 1-2 wt % of a gelling agent such as colloidal silicon dioxide. The suitability of a particular gel depends upon the compatibility of its constituents with both the oxybutynin and the permeation enhancer and any other components in the formulation.

The reservoir matrix should be compatible with oxybutynin, the permeation enhancer and any carrier therefor. The term "matrix" as used herein refers to a well-mixed composite of ingredients fixed into shape. When using an aqueous-based formulation, the reservoir matrix is preferably a hydrophilic polymer, e.g., a hydrogel. When using a non-aqueous-based formulation, the reservoir matrix is preferably composed of a hydrophobic polymer. Suitable polymeric matrices are well known in the transdermal drug delivery art, and

examples are listed in the above-named patents previously incorporated herein by reference.

A typical laminated system would comprise a polymeric membrane and/or matrix such as ethylene vinyl acetate (EVA) copolymers, such as those described in U.S. Pat. No. 4,144,317, preferably having a vinyl acetate (VA) content in the range of from about 9% up to about 60% and more preferably about 28% to about 60% VA. Polyisobutylene/oil polymers containing from 4-25% high molecular weight polyisobutylene and 20-81% low molecular weight polyisobutylene with the balance being an oil such as mineral oil or polybutynes may also be used as the matrix material.

The aforementioned patents describe a wide variety of materials which can be used for fabricating the various layers or components of the transdermal oxybutynin delivery devices according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

The amount of oxybutynin present in the therapeutic device and required to achieve an effective therapeutic result depends on many factors, such as the minimum necessary dosage of oxybutynin for the particular indication being treated; the solubility and permeability of the matrix, of the adhesive layer and of the rate-controlling membrane, if present; and the period of time for which the device will be fixed to the skin. The minimum amount of oxybutynin is determined by the requirement that sufficient quantities of oxybutynin must be present in the device to maintain the desired rate of release over the given period of application. The maximum amount for safety purposes is determined by the requirement that the quantity of oxybutynin present cannot exceed a rate of release that reaches toxic levels. The oral lethal dose discovered for rats is 1220 mg/kg.

When a constant oxybutynin delivery rate is desired, the oxybutynin is normally present in the matrix or carrier at a concentration in excess of saturation, the amount of excess being a

function of the desired length of the oxybutynin delivery period of the system. The oxybutynin may, however, be present at a level below saturation without departing from this invention as long as oxybutynin is continuously administered to the same skin or mucosa site in an amount and for a period of time sufficient to provide the desired therapeutic rate and delivery profile of oxybutynin delivery.

The permeation enhancer is dispersed through the matrix or carrier, preferably at a concentration sufficient to provide permeation-enhancing amounts of enhancer in the reservoir throughout the anticipated administration period. Where there is an additional, separate permeation enhancer matrix layer as well, as in FIGS. 3 and 4, the permeation enhancer normally is present in the separate reservoir in excess of saturation.

The preferred permeation enhancers of the present invention are a monoglyceride or a mixture of monoglycerides of fatty acids with a total monoester content of at least 51%. Fatty acids may be saturated or unsaturated and straight or chained, and include, for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid and palmitic acid. Monoglycerides are generally available as a mixture of monoglycerides, with the mixture deriving its name from the monoglyceride present in the greatest amount. Monoglyceride permeation enhancers include, for example, glycerol monooleate, glycerol monolaurate and glycerol monolinoleate. In a more preferred embodiment, the permeation enhancer is glycerol monooleate.

In addition to oxybutynin and a suitable permeation enhancer, which are essential to the invention, the matrix or carrier may also contain dyes, pigments, inert fillers, excipients and other conventional components of pharmaceutical products or transdermal devices known to the art.

In the present invention, oxybutynin is delivered at a therapeutically effective rate (that is, a rate that provides a desired therapeutic effect) and the permeation enhancer is delivered at a permeation-enhancing rate (that is, a rate that provides

increased permeability of the application site to the oxybutynin) for a predetermined time period and in the required delivery pattern.

A preferred embodiment of the present invention comprises a method of treating any disorder in which it is therapeutic to administer a therapeutically effective amount of one or more of the compounds of the present invention to a patient suffering from such disorder.

Another preferred embodiment of the present invention comprises a method of treating neurogenic bladder disorders, e.g., urinary frequency or incontinence. To be useful in treating a neurogenic bladder disorder. oxybutynin should be present in plasma at levels above about 0.5 ng/ml, preferably at levels above about 1.0 ng/ml and most preferably at levels of about 2.0 ng/ml. To achieve this result, oxybutynin is delivered at a therapeutic rate of at least about 40-200 μg per hour, but typically of at least 80 μg/hr, and more typically at about 80-160 μg/hr, for the treatment period, usually about 24 hours to 7 days.

The administration rate through the skin should be sufficient to minimize the size of the device. The size of the device of this invention can vary from less than 1 cm^2 to greater than 200 cm^2. A typical device, however, will have a size within the range of 5-50 cm^2. The delivery device containing the oxybutynin and a permeation enhancer is placed on a user such that the device is delivering oxybutynin in a therapeutically effective amount to the user to treat a neurogenic bladder disorder.

The length of time of oxybutynin presence and the total amount of oxybutynin in the plasma can be changed following the teachings of this invention to provide different treatment regimens. Thus, they can be controlled by the amount of time during which exogenous oxybutynin is delivered transdermally to an individual or animal.

The devices of this invention can be designed to effectively deliver oxybutynin for an extended time period of from several hours up to 7 days or longer. Seven days is generally the maximum time limit for application of a single device because the adverse affect of occlusion of a skin site increases with time and the normal cycle

of sloughing and replacement of the skin cells occurs in about 7 days. The transdermal therapeutic devices of the present invention are prepared in a manner known in the art, such as by those procedures, for example, described in the transdermal device patents listed previously herein. Having thus generally described the invention, the following specific examples describe preferred embodiments thereof.

DETAILED DESCRIPTION OF EXAMPLES

The devices for Example 1 were prepared as follows:

A. Formulation without a Permeation Enhancer

A formulation containing 30 wt % oxybutynin base in a matrix of EVA 40 (U.S.I. Chemicals, Illinois) was prepared by dissolving the oxybutynin base and EVA 40 in methylene chloride. The solution was poured onto a sheet of fluorocarbon diacrylate ("FCD")/polyester release liner to dry. The dried material was pressed to 5 mil (a. 0.1 mm) thickness between two sheets of FCD/polyester release liner at 75°C. The resulting film was laminated to a flexible cloth backing (spun laced polyester, 1.3 oz/yd^2), and 2.0 cm^2 discs were cut from the laminate.

B. Formulations with Permeation Enhancers

Formulations containing oxybutynin base at 30 wt %, and various permeation enhancers glycerol monolaurate, glycerol monooleate, and glycerol monolinoleate) at 25 wt % in a matrix of EVA 40 were prepared by dissolving the oxybutynin base, permeation enhancer and EVA 40 in methylene chloride. The same procedure as described above was then used to make the device.

The glycerol monooleate (GMO) used was Myverol® 18-99K glycerol monooleate (Eastman Kodak Chemicals), which has a glycerol monooleate content of 61% and a total monoester content of 93%, the glycerol monolinoleate (GMLO) used was Myverol® 18-92K glycerol monolinoleate, which has a glycerol monolinoleate content of 68% and a minimum total monoester content of 90%, and the glycerol monolaurate (GML) used was Grindtek® ML 90 glycerol monolaurate, which has a glycerol

monolaurate content of 90% and a minimum total monoester content of 90%.

C. Device with In-line Adhesive

Each of the oxybutynin matrix/cloth backing laminates were divided in half, and one half of each was laminated to 3M acylate transfer adhesive MSP 32589 (1.6 mil, an acrylate adhesive with 2-5% acid functionality). Before testing, each final laminate was equilibrated for at least 5 days to allow the enhancer and oxybutynin to partition into the contact adhesive. The edges of the devices with in-line adhesive were masked with polyester tape so that the oxybutynin reservoir edges were not exposed to the epidermis or solutions when they were tested.

The devices for Examples 2, 4 and 5 are prepared as follows:

A. Formulation containing GMO

A formulation containing 27 wt % oxybutynin base and 27 wt % GMO (Myverol® 18-99K glycerol monooleate) in a matrix of EVA 40 was prepared using a Brabender Mixer and a 50 cc mixing bowl. The EVA 40 was added to the mixing bowl and mixed until pellets were no longer visible. The oxybutynin base was slowly added to the mixing bowl. Mixing was continued for an additional 10 minutes after addition was complete. GMO was heated to 40°C and added very slowly to the mixing bowl. Addition time was approximately 45 minutes. The bowl was then closed and mixing continued for at least 20 minutes before removing the completed oxybutynin mix from the bowl.

The oxybutynin mix was calendared to 5 mil thickness between release liners (FCD/polyester). Five one-foot sections of the oxybutynin film were heat laminated to Medpar® backing (medium density polyethylene layer/aluminum polyester layer/EVA layer). Three of the oxybutynin film/backing laminates were laminated to 3M acrylate transfer adhesive MSP 1006 P.

EXAMPLE 1

The in vitro transdermal oxybutynin permeation rates through the epidermis of two human skin donors from devices described above were determined. For each device tested, the release liner was removed and the oxybutynin-releasing surface was placed against the stratum corneum side of a disc of human epidermis which had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon® holder of a release rate rod using nylon mesh and metal string. The rods were reciprocated in a fixed volume of receptor solution 0.05 M phosphate buffer, pH 6.5. The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

Results are summarized in the following table:

TABLE 1

	Permeation Enhancer	Average Transdermal Oxybutynin (Base) Permeation Rate $\mu g/cm^2/hr$ for 0-96 hrs
With adhesive	None (control)	1.21
	GML	3.74
	Myverol® 18-99K	3.09
	Myverol® 18-92K	2.40
Without adhesive	None Control	1.13
	GML	4.24
	Myverol® 18-99K	3.59
	Myverol® 18-92K	2.47

EXAMPLE 2

The in vitro transdermal oxybutynin permeation rates through the epidermis of five human skin donors from devices described above were determined as described in Example 1. The control formulation contained 30 wt % oxybutynin base (no permeation enhancer) in an EVA 40 matrix. No in-line adhesive was present. The other formulation

contained 28 wt % oxybutynin base and 28 wt % Myverol® 18-99K glycerol monooleate in an EVA 40 matrix. There was a 3M acrylate in-line adhesive present. This same device was used in the in vivo testing described in Examples 3 and 4. The results are summarized in the following table:

TABLE 2

Skin Donor	Control Without Permeation Enhancer $\mu g/cm^2/hr$	With Permeation Enhancer $\mu g/cm^2/hr$
1	4.7	15.4
2	3.1	6.8
3	2.6	9.4
4	2.5	4.7
5	2.6	5.4

EXAMPLE 3

This experiment was carried out using standard glass diffusion cells which consist of a donor compartment with a 4 ml capacity, and a receptor compartment with a 22 ml capacity. A circular piece of epidermis was placed in each diffusion cell (permeation area = 1.13 cm^2) in a horizontal position between a lower capped receptor compartment and an upper capped donor compartment. The receptor compartment has both a venting tube (uncapped) and a sampling port (capped). The stratum corneum side of the epidermis faced the donor compartment. An O-ring was positioned between the epidermis and the donor compartment, and a clamp held the compartments together. The receptor solution, 22 ml of 0.05 M phosphate buffer solution, pH 6.5, was added to each receptor compartment. The cells were placed in a temperature controlled water bath shaker at 35°C and allowed to come to temperature before the donor solution was added.

A total of five donor solutions were tested, and the donor volume was 0.2 ml in each case. The donor solutions tested were oxybutynin saturated in 0.05 M phosphate buffer solution, pH 6.5, oxybutynin saturated in mineral oil, oxybutynin saturated in a solution of 30% ethanol in phosphate buffer, oxybutynin saturated in a solution of 10.6% Myverol 18-99K glycerol monooleate in mineral

oil, and oxybutynin saturated in a solution of 10.6% glycerol monolaurate in mineral oil. All donor solutions were at pH 6.5.

At each time interval, the receptor solution was removed from the test cell and replaced with an equal volume of fresh receptor solution previously equilibrated at 35°C. The receptor solutions for each time interval were then assayed for oxybutynin, by HPLC (Zorbax Rx-C8, 15 cm x 4.6 mm ID, 5 μm, 30% acetonitrile/water, 0.06% dimethyloctylamine, 0.03% H_3PO_4, 220 nm, 1.0 ml/min), to calculate the permeation rate of oxybutynin through epidermis from the donor solution.

As can be seen in Figure 5, glycerol monolaurate and glycerol monolinoleate increased the permeation rate of oxybutynin, whereas ethanol showed the same permeation rate as the donor solution containing no permeation enhancer.

EXAMPLE 4

The in vivo plasma levels of oxybutynin were measured for two body sites. A 10 cm^2 device was worn on the penis for 10½ hours and two 10 cm^2 devices were worn on the inner thigh for 24 hours. A control sample was drawn before applying the systems. The device worn on the penis produced a plasma oxybutynin level of 2.0 ng/mL within 4 hours, and the levels varied between 1.4 and 2.1 ng/mL during the following 6½ hours of wearing. The systems worn on the inner thigh produced a plasma oxybutynin concentration of 0.9 ng/mL after 12 hours of wearing, and after 24 hours of wearing the level had reached 1.1 ng/mL.

The in vivo plasma oxybutynin concentration were also measured in two additional subjects who each wore two 10 cm^2 systems on the inner thigh. One subject achieved a plasma oxybutynin concentration of 2.0 ng/mL after 9 hours, and the plasma level was 1.7 ng/mL after 24 hours of wearing. The other subject achieved a plasma level of 0.7 ng/mL after 12 hours, and the plasma level was 0.8 ng/mL after 24 hours.

EXAMPLE 5

The residual oxybutynin in devices which had been worn by subjects was measured and compared to the oxybutynin content of devices which had not been worn. The results are summarized in the following table:

TABLE 3

Subject #	Site	Measured Drug Loss (mg/20 cm^2/day)
1	inner thigh	5.8
2	inner thigh	8.6
3	chest	6.7
4	abdomen	7.2
5	penis	19.2

Having thus generally described the present invention and described certain specific embodiments thereof including the embodiments that the applicants consider the best mode of practicing their invention, it will be readily apparent that various modifications to the invention may be made by workers skilled in the art without departing from the scope of this invention which is limited only by the following claims.

WHAT IS CLAIMED IS:

1. A device for the transdermal administration, at a therapeutically effective rate, of oxybutynin, which device comprises:

(a) a reservoir comprising a therapeutically effective amount of oxybutynin and a skin permeation-enhancing amount of a permeation enhancer;

(b) a backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in oxybutynin- and permeation enhancer-transmitting relation with the skin.

2. A device according to Claim 1 wherein the permeation enhancer is a monoglyceride or a mixture of monoglycerides of a fatty acids with a total monoesters content of at least 51%.

3. A device according to Claim 2 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

4. A device according to Claim 1 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

5. A device according to Claim 1 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

6. A device according to Claim 1 wherein the backing is permeable to water vapor.

7. A device according to Claim 1 wherein the permeation enhancer is glycerol monooleate and the reservoir further comprises a

matrix containing ethylene vinyl acetate copolymer having from about 9% to 60% vinyl acetate.

8. A device according to Claim 6 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir.

9. A device for the transdermal administration, at a therapeutically effective rate, of oxybutynin, which device comprises:

(a) a first reservoir comprising a therapeutically effective amount of oxybutynin and a skin permeation-enhancing amount of a permeation enhancer;

(b) a second reservoir comprising an excess of the permeation enhancer and substantially free of oxybutynin;

(c) a rate-controlling membrane between the first reservoir and the second reservoir;

(d) a backing on the skin-distal surface of the second reservoir; and

(e) means for maintaining the first and second reservoirs in oxybutynin- and permeation enhancer-transmitting relation with the skin.

10. A device according to Claim 9 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

11. A device according to Claim 9 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

12. A device according to Claim 9 wherein the backing is permeable to water vapor.

13. A device according to Claim 9 wherein the means for maintaining the reservoirs in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the first reservoir.

14. A device according to Claim 9 wherein the first reservoir also is an adhesive layer which functions as the means for maintaining the reservoirs in relation with the skin.

15. A device according to Claim 9 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

16. A device according to Claim 15 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

17. A method for the transdermal administration of oxybutynin, which method comprises:

(a) administering oxybutynin at a therapeutically effective rate to an area of skin; and

(b) simultaneously administering a permeation enhancer to the area of skin at a rate which is sufficient to substantially increase the permeability of the area to the oxybutynin.

18. A method according to Claim 17 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

19. A method according to Claim 18 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

20. A method according to Claim 17 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

21. A method according to Claim 17 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

22. A method according to Claim 17 wherein the backing is permeable to water vapor.

23. A method for treating neurogenic bladder disorders, the method comprising the step of placing a oxybutynin transdermal delivery device onto the skin of a person, the oxybutynin transdermal delivery device comprising:

(a) a reservoir comprising oxybutynin in an amount sufficient to provide treatment of symptoms of a neurogenic bladder for a predetermined period of time and a permeation enhancer in a skin permeation-enhancing amount;

(b) a backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in oxybutynin- and permeation enhancer-transmitting relation with the skin.

24. A method according to Claim 23 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

25. A method according to Claim 24 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

26. A method according to Claim 23 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for the predetermined period of time.

27. A method according to Claim 23 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

28. A method according to Claim 23 wherein the backing is permeable to water vapor.

29. A method according to Claim 23 wherein the permeation enhancer is glycerol monooleate and the reservoir further comprises a matrix comprising ethylene vinyl acetate copolymer having from about 9% to 60% vinyl acetate.

30. A method according to Claim 29 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir.

31. A method for treating neurogenic bladder disorders, the method comprising the step of placing a oxybutynin transdermal delivery device onto the skin of a person, the oxybutynin transdermal delivery device comprising:

(a) a first reservoir comprising oxybutynin in an amount sufficient to provide treatment of symptoms of a neurogenic bladder for a predetermined period of time and a permeation enhancer in a skin permeation-enhancing amount;

(b) a second reservoir comprising an excess of the permeation enhancer and substantially free of oxybutynin;

(c) a rate-controlling membrane between the first reservoir and the second reservoir;

(d) a backing on the skin-distal surface of the second reservoir; and

(c) means for maintaining the first and second reservoirs in oxybutynin- and permeation enhancer-transmitting relation with the skin.

32. A method according to Claim 31 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

33. A method according to Claim 31 wherein oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

34. A method according to Claim 31 wherein the backing is permeable to water vapor.

35. A method according to Claim 31 wherein the means for maintaining the reservoirs in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the first reservoir.

36. A method according to Claim 31 wherein the first reservoir also is an adhesive layer which functions as the means for maintaining the reservoirs in relation with the skin.

37. A method according to Claim 31 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

38. A device according to Claim 37 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

FIG. 1

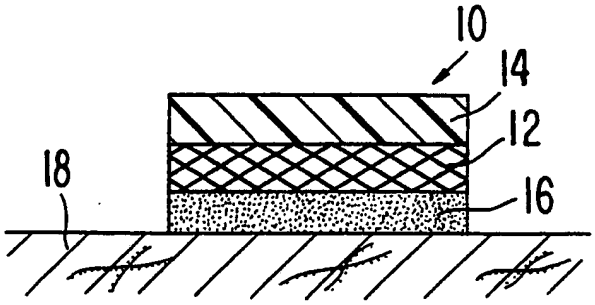


FIG. 2

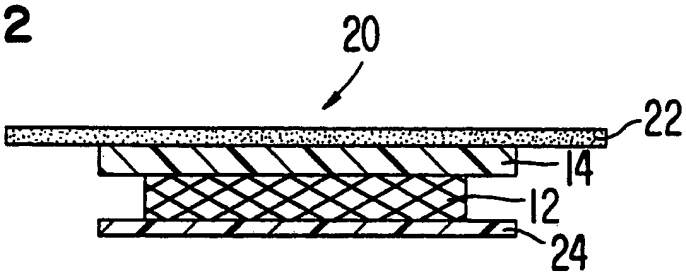


FIG. 3

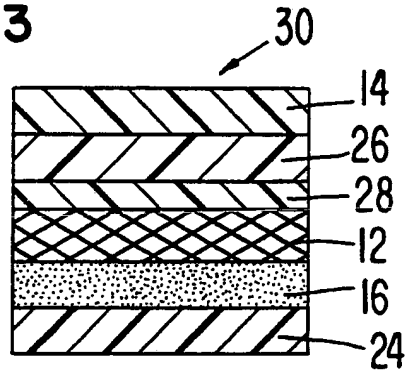


FIG. 4

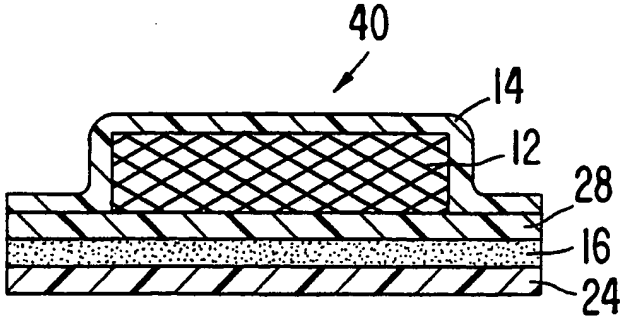
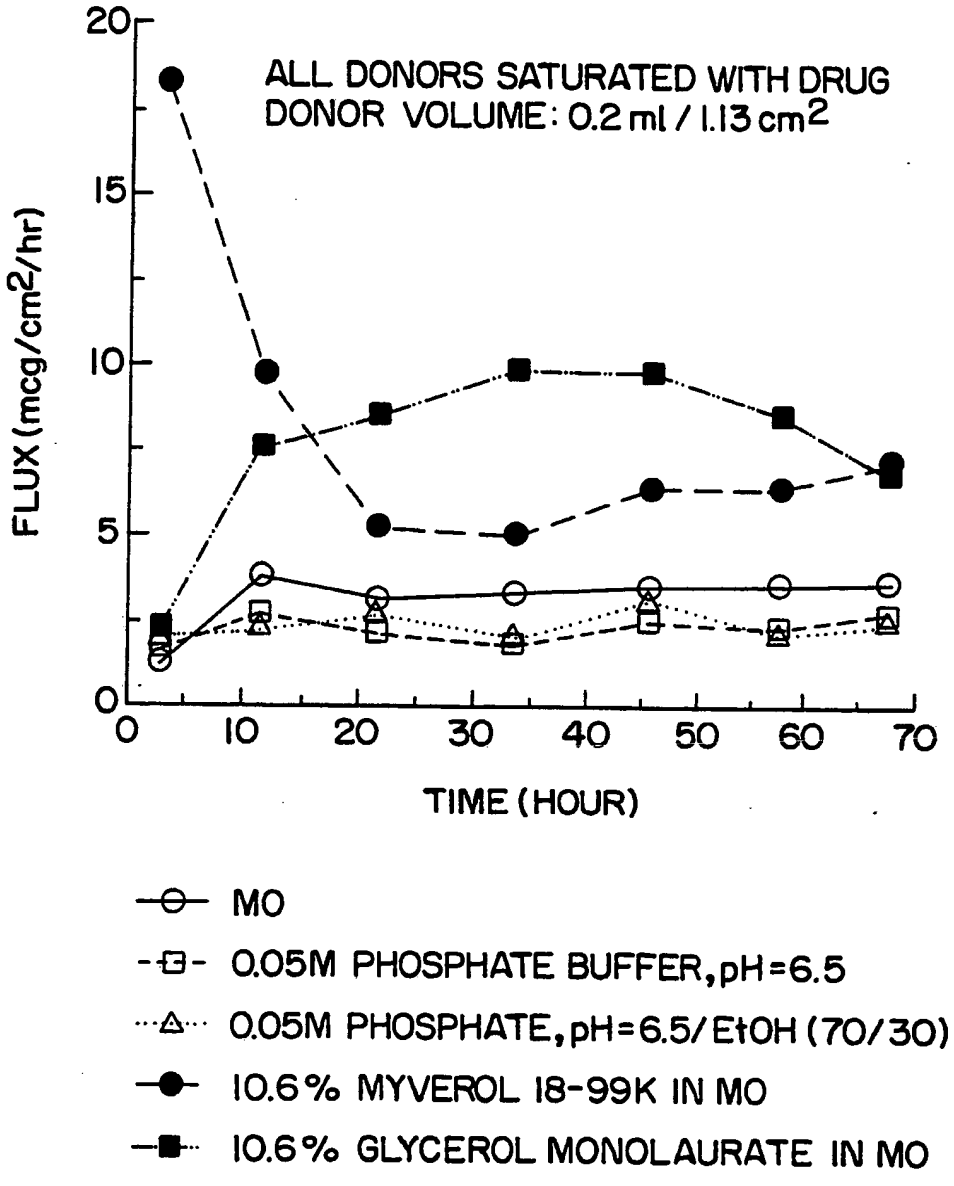


FIG. 5


ALL DONORS SATURATED WITH DRUG
DONOR VOLUME: 0.2 ml / 1.13 cm2
FLUX (mcg/cm2/hr)
TIME (HOUR)
0
5
10
15
20
0
10
20
30
40
50
60
70
MO
0.05M PHOSPHATE BUFFER, pH=6.5
0.05M PHOSPHATE, pH=6.5/EtOH (70/30)
10.6% MYVEROL 18-99K IN MO
10.6% GLYCEROL MONOLAURATE IN MO

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04518

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/135; A61K9/70; A61K47/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 250 125 (SMITH & NEPHEW) 23 December 1987 cited in the application see claims	1-38
A	US,A,4 747 845 (B.KOROL) 31 May 1988 cited in the application see claims see column 9, line 46	1-38
A	DATABASE WPIL Week 9219, Derwent Publications Ltd., London, GB; AN 92-157308 (19) & JP,A,04 099 719 (RIDO CHEMICAL KK) 31 March 1992 see abstract	1-38

-/--

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 AUGUST 1993	31. 08. 93 31.08.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	WO,A,9 220 377 (ALZA CORPORATION) 26 November 1992 see claims see example 5	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/04518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 17-37 are directed to a method of treatment of the human body by therapy (Rule 39.1(IV)PCT), the search has been carried out and based upon the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304518
SA 74136

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0250125	23-12-87	AU-B- 609398	02-05-91
		AU-A- 7378987	10-12-87
		CA-A- 1272922	21-08-90
		GB-A- 2191943	31-12-87
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		US-A- 4784857	15-11-88
US-A-4747845	31-05-88	US-A- 4563184	07-01-86
		US-A- 4857334	15-08-89
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		CA-A- 1245158	22-11-88
		EP-A,B 0138740	24-04-85
		EP-A- 0344090	29-11-89
		JP-A- 60150755	08-08-85
		US-A- 4725271	16-02-88
WO-A-9220377	26-11-92	AU-A- 2010392	30-12-92

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/22, 31/215

A1

(11) International Publication Number: WO 96/12477

(43) International Publication Date: 2 May 1996 (02.05.96)

(21) International Application Number: PCT/FI94/00474

(22) International Filing Date: 21 October 1994 (21.10.94)

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(74) Agent: OY JALO ANT-WUORINEN AB; Iso Roobertinkatu 4-6 A, FIN-00120 Helsinki (FI).

(81) Designated States: AM, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LT, LV, NO, NZ, PL, RO, RU, SI, SK, TJ, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: CONTROLLED RELEASE ORAL DELIVERY SYSTEM CONTAINING OXYBUTYNIN

(57) Abstract

The present invention concerns a controlled release drug delivery system for oxybutynin, its manufacture and use. The drug delivery system comprises oxybutynin in combination with a controlled release excipient comprising about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of 1:3 to 3:1, a cationic crosslinking agent for the said hydrophilic material, in an amount of 1 to 20 % by weight, and 20-79 % by weight of an inert filler.

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GA	Gabon				

Controlled release oral delivery system containing oxybutynin.

The present invention relates to controlled or extended release delivery systems for the treatment of disorders responsive to the action of an antispasmodically active agents, especially for the treatment of a neurogenic bladder, a method of preparation of the delivery systems as well as method of using them.

Oxybutynin and its salts, in particular the hydrochloride (hereinafter oxybutynin) is a musculotropic antispasmodic drug with moderate anticholinergic, systemic analgesic and local anaesthetic action. Its relaxant effect on smooth muscle is based on antagonism of a process distal to the neuromuscular junction (papaverine-like effect) and on anticholinergic action on the blockage of muscarine-type receptors. Oxybutynin chloride has been in clinical use for twenty years and it is indicated for the relief of symptoms associated with voiding in patients with an uninhibited neurogenic and reflex neurogenic bladder. It is also used to suppress gastric acid secretion, to relieve post-transurethral vesical pain and spasm in the gastrointestinal tract, to control detrusor dysfunction and to facilitate catheterization of the urinary bladder in myelomeningocele patients. The drug is effective when given orally.

Chemically, oxybutynin hydrochloride (DL-racemic form of 4-diethylamino-2-butynyl-phenyl-cyclohexylglycolate hydrochloride) is a tertiary amine. It is rapidly absorbed from the gastrointestinal tract following oral administration and its pharmacological action starts within one hour. The duration of action of the drug is three to six hours.

It has been established that after the administration of oxybutynin hydrochloride (5 mg dose tablet), the maximum concentration of unmetabolized oxybutynin in plasma was

reached within 1 h, and the elimination half-life was about 2.5 h. Due to the relatively rapid elimination of the active agent from the blood, conventional treatment with oxybutynin has comprised administering oxybutynin in a dose of 5 mg (calculated as the hydrochloride) twice or three times daily, the recommended maximal dose of oxybutynin being 20 mg per day.

In conventional treatment, the administration of oxybutynin is accompanied by a high initial peak concentration in the blood with associated side effects. Furthermore, the frequent need to administer the drug in order to maintain or restore the necessary concentration of active agent in the blood is cumbersome and consequently has a tendency to reduce patient compliance.

Consequently, there is a need for an oxybutynin preparation with a sustained action. Especially there is a need for a preparation which allows for a reduction of the peak initial drug concentration in the blood and which provides for an even and substantially extended effect. Such a preparation would readily allow for a once-a-day treatment with a single oral dose.

According to the invention the afore mentioned aim has been reached by combining oxybutynin or a pharmaceutically acceptable salt thereof, with an excipient allowing the controlled and extended, even release of the active agent over a period of time exceeding 24 hours while simultaneously reducing the initial peak concentrations of active agent in the blood of the patient.

Thus the invention provides a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin,

or a pharmaceutically acceptable salt thereof,

- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

The excipient used in the composition according to the invention thus comprises as one component a hydrophilic material or gelling system comprising on the hand a heteropolysaccharide, and on the other hand a homopolysaccharide which is capable of crosslinking the heteropolysaccharide in an aqueous fluid, such as in a gastric fluid, the ratio between the two types of saccharides being from about 3:1 to 1:3.

The heteropolysaccharide is a water soluble saccharide containing two or more kinds of sugar units, and it has excellent swelling properties. According to a preferred embodiment it comprises a xanthan gum, or a derivative thereof. Such derivatives are deacylated xanthan gum, the carboxymethyl ether and propylene glycol ester.

In the preferred embodiment, the homopolysaccharide comprises one or more galactomannans, and especially galactomannas with a higher ratio of mannose to galactose, e.g. locust bean gum. Other polysaccharides are e.g. guar gum and hydroxypropyl guar gum.

The ratio between heteropolysaccharide and homopolysaccharide is preferably approximately 1:1.

In addition the excipient contains an inert filler or diluent, which suitably is a monosaccharide, disaccharide or polyhydric alcohol, such as sucrose, dextrose, lactose, fructose, xylitol, sorbitol, and microcrystalline cellulose, or mixtures thereof.

The excipient used in the composition according to the invention contains in addition a cationic crosslinking agent which is capable of crosslinking the hydrophilic material, when this is exposed to gastrointestinal fluids, thus strengthening the gel structure and preventing an initial burst of the drug when exposed to a gastrointestinal environment. The amount of cationic crosslinking is at the most about 20 % by weight, such as from bout 1 to 20, especially about 5 to 15 % by weight.

The cationic crosslinking agent can be a mono- or multivalent salt, preferably an inorganic salt such as alkali and/or alkaline earth metal salt, such as sodium, potassium, litium, calcium, magnesium chloride, bromide, sulfate, borate, citrate, acetate, lactate, carbonate, bicarbonate. The cationic crosslinking agent is preferably divalent, such as in calcium sulfate, or it is sodium chloride.

Controlled release excipients containing a combination of hetero- and homopolysaccharides as defined above with inert diluents, have been described in the US patents 4,994,276, 5,128,143, and 4,135,757.

In a preferred embodiment the excipient contains about 25 to 50, especially about 25 to 35 % by weight of the hydrophilic material or gelling system, about 5 to 15 % by weight of cationic crosslinking agents, and about 35 to 70, especially about 50 to 70 % by weight of inert diluent.

The ratio of oxybutynin (calculated as its hydrochloride) to hydrophilic material is preferably about 1:5 to 1:15. A suitable amount of oxybutynin in a single dose, such as in a tablet, is about 5 to 20 mg, especially about 10 mg. A suitable daily dose of opxybutynin is from about 0.05 to 0.25 mg/kg body weight, especially appr. 0.12 mg/kg body weight.

The drug delivery system according to the invention can be made by first dry blending the ingredients for the excipient, and then granulating the mixture in the presence of small amount of fluid, such as water. The obtained granulate is therafter combined with the active ingredient for example by simple dry-blending, or by using wet granulation techniques, using e.g. water as the granulating fluid.

According to an embodiment of the invention, a suitable lubricant, known per se, can be added to the excipient and drug components to be combined. The choice of lubricants is well known in the art, and magnesium, calcium and sodium stearate may be mentioned. A suitable amount of lubricant is appr. 0,5 to 3 % by weight.

The drug-excipient mixture prepared may be compressed to tablets according to conventional tablet formation techniques. The blend may also be used as pellets, as a granulate or powder, or filled in capsules. The dosage formed obtained may be coated using any suitable coating system. Such coating systems and coating techniques are well known in the art.

According to the invention it is possible to add to the composition further agents and additives, e.g. hydrophobic agents for regulating the hydration of the product, for example by including polymeric cellulose derivatives, such as alkyl celluloses, polymeric acrylic and methacry-

lic acid derivatives, waxes, oils etc. usually in amounts amounting to about 1 to 20 % by weight. Such an addition replaces part of the inert diluent. The hydrophobic agents are as such well known in the art, and a number of them are commercially available. It is also possible to add release rate decreasing substances to the mixture of drug and excipient, for example microcrystalline cellulose in an amount of about 1 to 10 % by weight.

The present invention also concerns a method for treating a subject of a condition responsive to the action of an antispasmodically active agent, such as voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction, especially of neurogenic bladder, the method comprising administering to the subject for oral ingestion a delivery system, especially a tablet, according to the invention as defined above.

The invention also concerns a method of maintaining, in a human subject, a therapeutically sufficient blood level concentration of oxybutynin or of an active metabolite thereof, such as N-desethyl oxybutynin, for an extended period of time, the method comprising administering orally to the said subject a controlled release delivery system according to the invention, as defined above, especially a tablet containing 5 to 20 mg of oxybutynin. Preferably a therapeutically sufficient blood level concentration is maintained for at least about 24 hours after administration of a single dose of oxybutynin, such as a single dose of about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight, of oxybutynin or a salt thereof, e.g. the hydrochloride. The administration of a daily single dose of a 10 mg controlled release oxybutynin tablet gave blood level concentrations of oxybutynin of at least about 0.5 ng/ml, such as 0.5 to 2.0 ng/ml for a period of at least about 24 hours, the value following

the peak value being in the area of about 0.5 to 1.0 ng/ml, as is evident from the test report.

The following examples illustrate the invention, however, without limiting the scope thereof. Parts and percentages are by weight, unless otherwise stated.

Examples 1 - 2:

In Examples 1-2, controlled release excipients in accordance with the present invention were first prepared, the oxybutynin being added subsequently, and the final mixture then being tableted.

The excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, calcium sulfate, and dextrose in a high speed mixer/granulater for 2 minutes. While running choppers/impellers, the requisite amount of water was added to the dry blended mixture, and granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a LOD (loss on drying) of less than about 10% by weight (e.g. 4-7% LOD). The granulation was then milled using 20 mesh screens. The ingredients of the granulations of Examples 1-2 are set forth in Table 1 below:

TABLE 1

Preparation of sustained-release excipient

Component	% - Ex. 1	% - Ex. 2
1. Xanthan Gum	25	25
2. Locust Bean Gum	25	25
3. Dextrose	40	30
4. Calcium Sulfate	10	20
5. Water	10*	10*

*Removed during processing.

Next, the excipient prepared as detailed above was dry blended with the desired amount of oxybutynin HCl in a V-blender for 10 minutes. A suitable tableting lubricant (Pruv®, sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc) was added, and the mixture was blended for another 5 minutes. This final mixture was compressed into tablets. The ingredients of the tablets of Examples 1-2 are set forth in Table 2 below:

TABLE 2

Tablet formulation - Examples 1-2

Component	% - Ex. 1	% - Ex. 2
1. Excipient	93.8	93.8
2. Oxybutynin HCl	4.7	4.7
3. Sodium stearyl fumarate	1.5	1.5
Tablet weight (mg)	213.2	213.2
Hardness (Kp)	3.3	1.4

Examples 3-4:

In Examples 3-4, a controlled release excipient was prepared in accordance with the procedures set forth for Examples 1-2. The ingredients of the sustained release matrix of Examples 3-4 are set forth in Table 3 below:

TABLE 3

Component	% - Ex. 3	% - Ex. 4
1. Xanthan Gum	15	15
2. Locust bean Gum	15	15
3. Dextrose	60	60
4. Calcium Sulfate	10	10
5. Water	10*	10*

*Revomed during prosessing.

Thereafter, oxybutynin tablets were prepared in accordance with the procedure set forth in Examples 1-2. The ingredients of the tablets of Examples 3-4 are set forth in Table 4 below:

TABLE 4

Component	% - Ex. 3	% - Ex. 4
1. Excipient	95.7	93.0
2. Oxybutynin HCl	2.9	5.6
3. Sodium stearyl fumarate	1.4	1.4
Tablet weight (mg)	348.3	179.3
Hardness (Kp)	10.4	3.3

In Example 3, the drug:gel ratio is about 1:10. In Example 4, the drug:gel ratio is about 1:5. By "gel" it is meant the combined weight of xanthan gum and locust bean gum.

TEST REPORT

A bioequivalence study was carried out to assess the bioavailability of oxybutynin from a delivery system according to the invention, using as a reference system an ordinary 5 mg oxybutynin chloride containing tablet, after a single peroral dose of 10 mg of oxybutynin chloride.

The study was performed as a balanced, randomized, three-period cross-over study on 24 healthy volunteers.

Pharmacokinetics

From serum concentrations of oxybutynin and its metabolite N-desethyl oxybutynin the following pharmacokinetic parameters were calculated:

- AUC_{0-t} using the linear trapezoidal rule (t was the last detectable concentration).
- C_{max} and t_{max} were used as measured

The individual and mean serum time-concentration curves for both oxybutynin and its metabolite N-desethyl oxybutynin were provided.

The pharmacokinetic parameters were calculated and curves created using the Siphar program.

Fourteen (14) blood samples (10 ml each) were taken during each study period according to the following schedule: 0 (pre-drug), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours following drug administration. A total of 420 ml blood was taken over the three study phases, exclusive of pre- and post-clinical blood work (30 ml).

All urine excreted during 24 h after administration of the drug was collected as follows: one sample was taken before administration (blank sample); thereafter, samples in fractions of four hours up to 12.0 h after administration (0.0-4.0 h, 4.0-8.0 h and 8.0-12.0 h), and in a fraction of twelve hours up to 24.0 h (12.0-24.0 h).

Urine fractions were measured by volume, and aliquots of 2-3 ml separated into duplicate polypropylene tubes, frozen immediately and stored at -20°C for later examination.

Evaluations

The data from this study was analyzed by comparing the pharmacokinetic parameters calculated for the controlled release tablet (test preparation) to those for the ordinary tablet (reference preparation).

Analytical methods

Analysis of oxybutynin and its metabolite N-desethyl oxybutynin in serum were carried out by a capillary gas chromatographic method using mass selective detector. The quantification limit of the method was 0.2 ng/ml for unchanged oxybutynin and 2.5 ng/ml for the metabolite. The method is linear from 0.2 ng/ml to 30 ng/ml for oxybutynin and from 2.5 to 150 ng/ml for N-desethyl oxybutynin, respectively.

Results

There were no statistically significant differences in the extent of oxybutynin in serum after administration of the controlled release tablet (Md AUC_{0-t}= 17.02 ng/ml*h) compared to that after intake of two 5 mg ordinary tablets (the reference preparation, Md AUC_{0-t}= 15.86 ng/ml*h).

The peak serum concentration of oxybutynin after the test controlled release tablet (Md C_{max}= 2.13 ng/ml) was however significantly lower and it was reached significantly later (Md t_{max}= 1.5 h) than those after administration of the reference tablets (Md C_{max}= 6.86 ng/ml, Md t_{max}= 0.75 h). This is also shown in the appended Figures 1 and 2. In these Figures, Fig. 1 shows the mean serum concentration of oxybutynin as a function of time after administartion of a 10 mg controlled release tablet of the invention, and 2 * 5 mg conventional tablets. Fig. 2 shows the serum concentration of the metabolite, N-desethyl oxybutynin after the said administration.

The clinical importance of the extended release pattern of the controlled release tablet was demonstrated by statistically significantly less anticholinergic side-effects compared to the conventional tablet. Furthermore, the high and persistent levels of the active metabolite of oxybutynin for the whole 24 h study period reflects the extended release characteristics of the 10 mg controlled release tablet.

In summary,

1. The controlled release tablet of the invention gave a reliable pharmacokinetic profile of an extended release formulation covering the 24-hour study period.

2. There were no statistically significant differences in the AUC of oxybutynin in serum after administration of the test controlled release tablet compared to that after intake of two 5 mg ordinary tablets.

3. The controlled release tablet can be considered a successful and clinically bioequivalent formulation when lower peak concentrations of oxybutynin in serum are desirable to diminish anticholinergic side-effects of oxybutynin.

Claims:

1. A controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

2. The delivery system according to claim 1, wherein the the ratio of oxybutynin to hydrophilic material is about 1:5 to 1:15.

3. The delivery system according to claim 1 wherein the oxybutynin is in the form of its hydrochloride salt.

4. The delivery system according to claim 3 in the form of a tablet containing from 5 to 20 mg of oxybutynin hydrochloride.

5. The delivery system according to claim 3 in the form of a tablet containing about 10 mg of oxybutynin hydrochloride.

6. A method of making a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising providing a controlled release excipient by combining

- about 15 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1, with
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight, and with
- about 20 - 79 % by weight of an inert filler,

combining said obtained controlled release excipient with oxybutynin, or a pharmaceutically acceptable salt thereof in an amount as to provide a ratio of oxybutynin to hydrophilic material from about 1:2 to 1:25, and, optionally using pharmaceutically acceptable adjuvants, forming the obtained mixture into a solid dosage form.

7. The method according to claim 6, wherein oxybutinin is used as its hydrochloride salt, the ratio of oxybutynin to hydrophilic material being about 1:5 to 1:15.

8. The method according to claim 7 wherein the mixture is compressed into tablets each containing from 5 to 20 mg, advantageously about 10 mg of oxybutynin hydrochloride.

9. Use of oxybutynin or its pharmaceutically acceptable salt for the preparation of an oral drug delivery system according to claim 1, providing extended and even release of the active agent over a period of time of at least 24 hours, for the treatment of disorders responsive to the effect of an antispasmodically active agent.

10. Use oxybutynin or its salt according to claim 9 for the preparation of a drug delivery system for the treatment of a neurogenic bladder.

11. A method for treating a subject for relief of a condition responsive to the action of an antispasmodically active agent, the method comprising administering to the subject for oral ingestion a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
- about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
- about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

12. The method according to claim 11 wherein the condition to be treated is selected from the group consisting of voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction.

13. The method according to claim 12, wherein the condition to be treated is neurogenic bladder.

14. The method according to claim 11, wherein the delivery system is a tablet containing from about 5 to 20 mg of oxybutynin hydrochloride.

15. The method according to claim 11 wherein oxybutynin hydrochloride is adminstered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

16. A method for maintaining a therapeutically sufficiently high blood level concentration of oxybutynin or of an active metabolite thereof, in a human subject, for an extended period of time, the method comprising administering orally to the subject a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

17. The method according to claim 16 wherein the extended period of time is at least about 24 hours.

18. The method according to claim 16 or 17 wherein oxybutynin hydrochloride ia administered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

FIG. 1

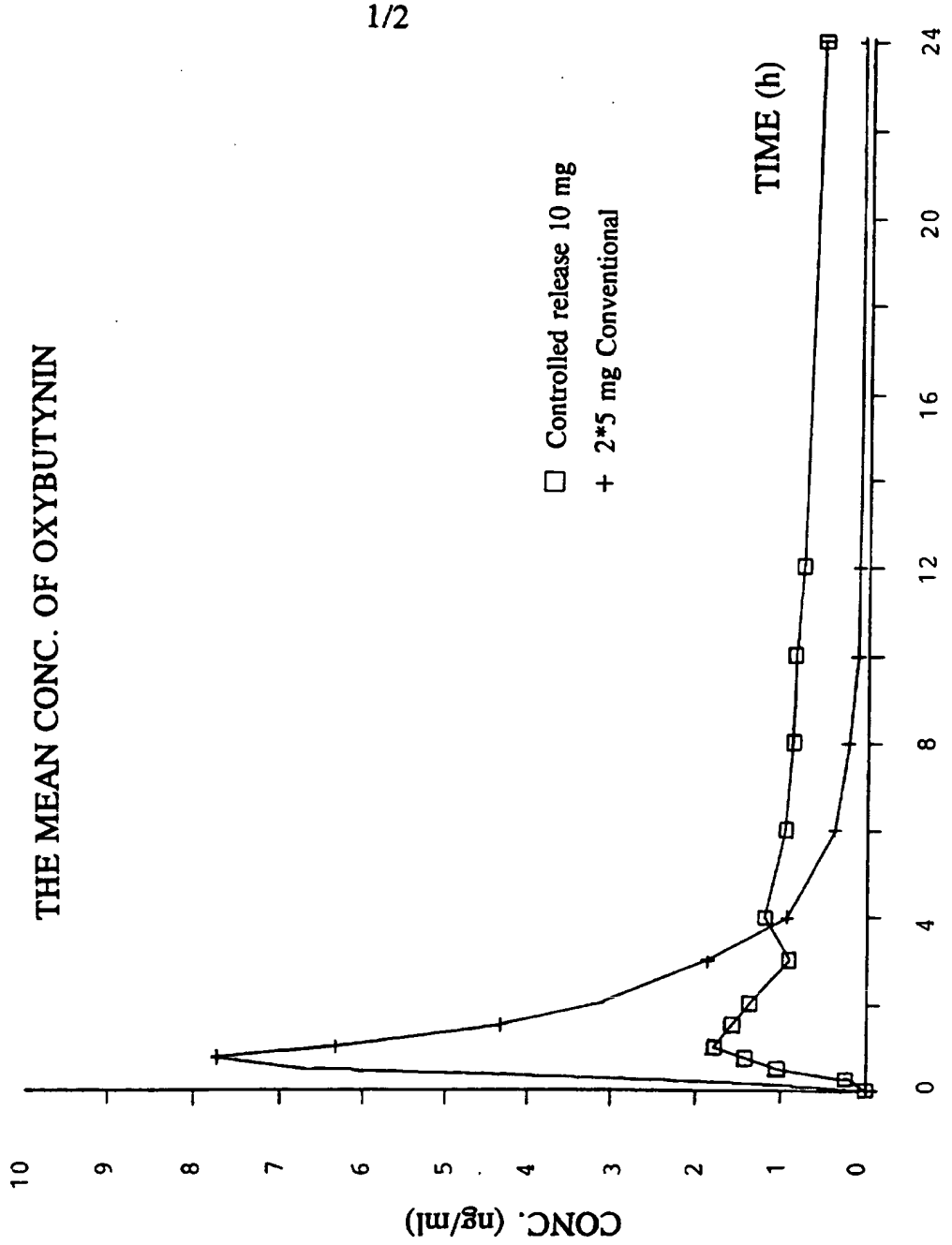
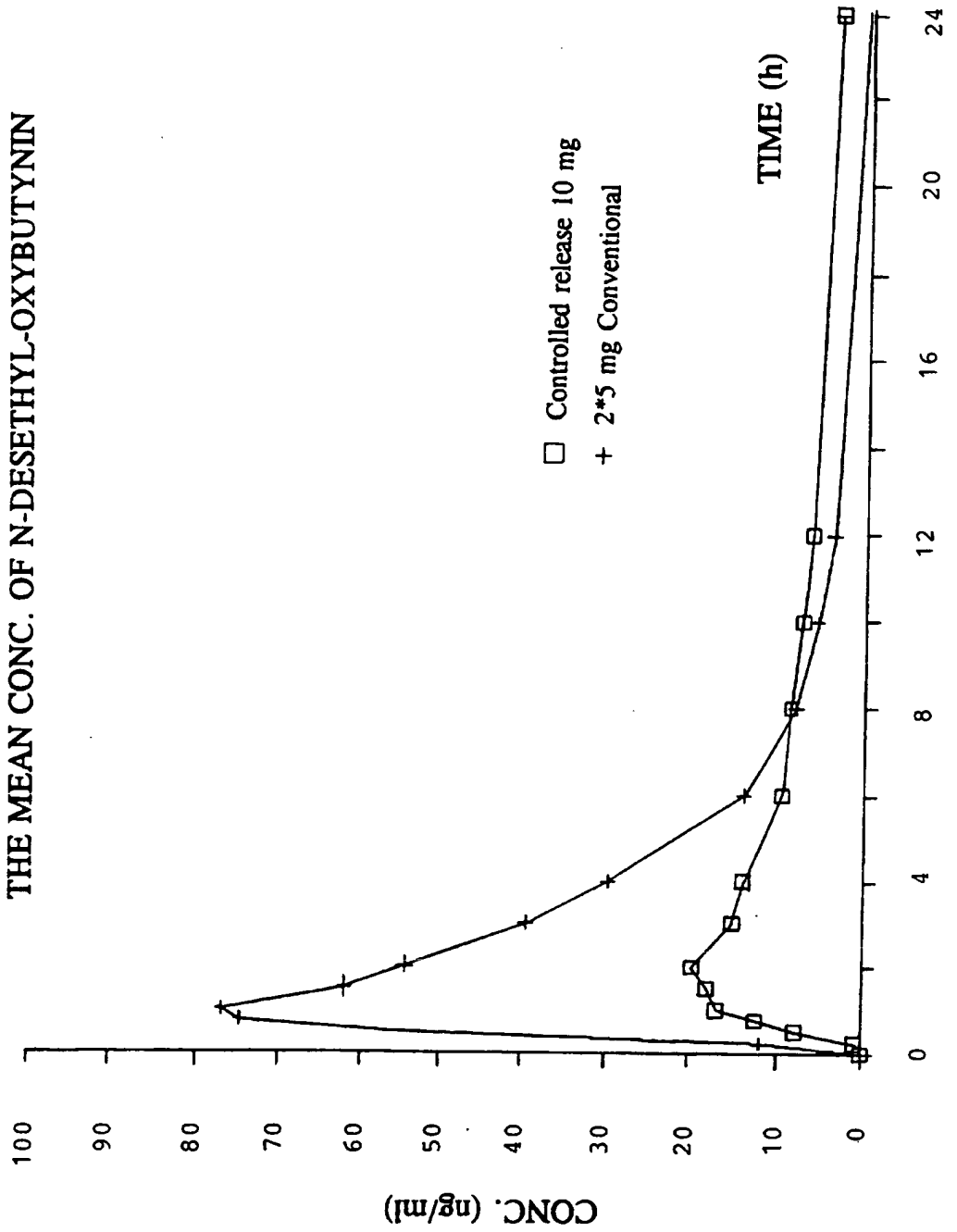


FIG.2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/22, A61K 31/215
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US, A, 5399359 (ANAND R. BAICHWAL), 21 March 1995 (21.03.95) --	1-10
X	US, A, 5169639 (ANAND R. BAICHWAL ET AL), 8 December 1992 (08.12.92), claims --	1-10
X	US, A, 5135757 (ANAND R. BAICHWAL ET AL), 4 August 1992 (04.08.92), column 6, line 49 - column 10, line 9, claims --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1995	13 -06- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0497977 (NIPPON SHINYAKU CO., LTD.), 12 August 1992 (12.08.92), column 7, line 22 - line 27, examples 4-6	1-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/95

International application No.
PCT/FI 94/00474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5399359	21/03/95	NONE	
US-A- 5169639	08/12/92	AU-B- 623182	07/05/92
		AU-A- 4305789	18/04/90
		DE-T- 68907835	11/11/93
		EP-A,A,A 0360562	28/03/90
		SE-T3- 0360562	
		ES-T- 2059778	16/11/94
		JP-T- 4501713	26/03/92
		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
		US-A- 5128143	07/07/92
		US-A- 5135757	04/08/92
		US-A- 5171440	15/12/92
		WO-A- 9003165	05/04/90
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		ES-T- 2059778	16/11/94
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		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
		US-A- 5128143	07/07/92
		US-A- 5169639	08/12/92
		US-A- 5171440	15/12/92
		WO-A- 9003165	05/04/90
EP-A1- 0497977	12/08/92	DE-D- 69017915	00/00/00
		US-A- 5368861	29/11/94
		AT-T- 119766	15/04/95
		WO-A- 9106281	16/05/91

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01N 33/18 — A1

(11) International Publication Number: **WO 98/03067**

(43) International Publication Date: 29 January 1998 (29.01.98)

(21) International Application Number: PCT/US97/12155

(22) International Filing Date: 14 July 1997 (14.07.97)

(30) Priority Data:
60/020,995 19 July 1996 (19.07.96) US

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(74) Agents: LEMACK, Kevin, S. et al.; Nields, Lemack & Dingman, Suite 8, 176 E. Main Street, Westboro, MA 01581 (US).

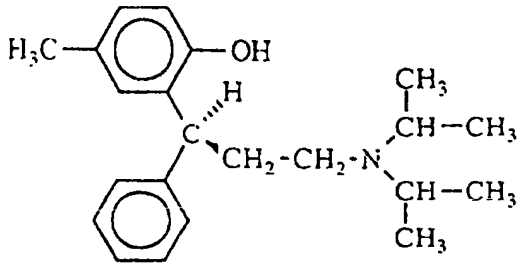
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: S(-)-TOLTERODINE IN THE TREATMENT OF URINARY AND GASTROINTESTINAL DISORDERS

(57) Abstract

The S-isomer of a compound represented by formula (I) and pharmaceutically acceptable salts thereof is disclosed as being useful for treating urinary disorders, including urinary incontinence, and gastrointestinal disorders, including gastrointestinal hyperactivity.



(I)

S(-)-tolterodine

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AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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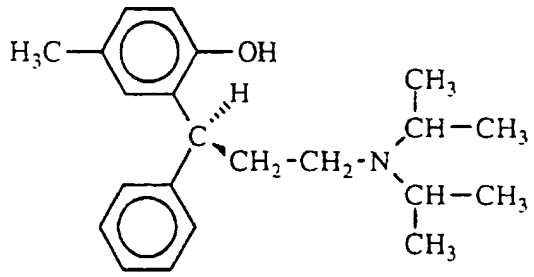
S(-)-TOLTERODINE IN THE TREATMENT OF URINARY AND GASTROINTESTINAL DISORDERS

FIELD OF THE INVENTION.

This invention relates to a compound named S(-)-tolterodine and having the formula:



S(-)-tolterodine

Specifically, the invention relates to processes for preparing S-tolterodine, to a method for treating urinary disorders, including urinary incontinence and a method for treating gastrointestinal disorders, including gastrointestinal hyperactivity, using the compound S-tolterodine and to pharmaceutical compositions containing S-tolterodine.

The generic name TOLTERODINE (CAS-124937-51-1; INN) refers to the R-enantiomer of the drug. In this document, the racemate and the optically active isomers of the compound are referred to as RS-tolterodine (or RS-TOL), S-tolterodine (or S-TOL), and R-tolterodine (or R-TOL).

BACKGROUND OF THE INVENTION.

R-tolterodine has been shown to reduce bladder pressure in cats and is presently undergoing clinical testing for inhibitory activity in patients suffering from detrusor overactivity (urinary incontinence). R-TOL exerts a spasmolytic effect on bladder smooth muscle by inhibiting the action of acetylcholine on smooth muscle. R-TOL is selective for muscarinic receptors over nicotinic receptors and as a result, no blocking

effects are observed at skeletal neuromuscular junctions. Like all other antimuscarinic compounds, R-TOL causes dry mouth, blurry vision, tachycardia and possibly also memory impairment.

R-TOL relaxes urinary bladder smooth muscle and in animals with conditions characterized by increased bladder contractions, cystometric studies have demonstrated that R-TOL has beneficial effects. R-TOL may therefore be useful in the treatment and prevention of incontinency and frequent voluntary urination in patients. The efficacy of R-TOL in the bladder has been attributed to its antimuscarinic effects on the detrusor muscle. Because of its antimuscarinic activity, mydriasis (dilated pupils), xerostomia (dry mouth), tachycardia (fast heart beats) and impaired normal urinary voiding, which mechanisms all involve muscarinic cholinergic receptors, are obvious and reported side effects for R-TOL (Ekström et al., J. Urol. 1995, Suppl.4: 394A and Stahl et al. 1995, Neurourol Urodyn.14: 647-655).

Pharmacological studies of the individual enantiomers of tolterodine have now been performed and have suggested that the R-TOL indeed is the efficacious enantiomer on muscarinic receptors. Thus, it was concluded that the cholinergic antagonism of racemic tolterodine (RS-TOL) could be attributed mainly to the activity of R-TOL. The rank order of potency of racemic tolterodine and its enantiomers for antimuscarinic activity is: R-TOL was greater or equal to RS-TOL, which was much greater than S-TOL, with S-TOL being approximately one or more orders of magnitude less potent than R-TOL.

SUMMARY OF THE INVENTION

It has now unexpectedly been found that S-TOL has outstanding non-cholinergic spasmolytic activities, while being practically devoid of anticholinergic activity. It has furthermore unexpectedly been found that S-TOL provides weak sedative effects. S-TOL therefore will offer superior treatment for urinary disorders, including urinary incontinence and for gastrointestinal disorders, including gastrointestinal hyperactivity, while being devoid of the anticholinergic side effects that reside in R-TOL.

While the optically pure R-TOL provides medical treatment in patients with urinary incontinence that arises from one single cause, namely muscarinic hyperactivity, it was found that the optically pure S-TOL provides spasmolytic activity against urinary and intestinal spasms that arise from various mechanisms. S-TOL is particularly useful in patients where urinary incontinence is caused by non-cholinergic mechanisms or in patients, where antimuscarinic side effects are not acceptable (for example in the elderly, where antimuscarinic side effects have unacceptable effects on memory). Non-cholinergic spasmogenic mechanisms include but are not limited to scars (i.e. from childberth or surgical interventions) causing detrusor pacemaker activity, release of thromboxane, release of platelet activating factor and other non-muscarinic spasmogens.

Chemically, S-TOL is S(-)-2-[α[2-(diisopropylamino)ethyl] benzyl]-*p*-cresol.

The active compound of this invention is S-TOL. The synthetic preparation is described in European Pat. Appl. EP 325571 A1, the disclosures of which are hereby incorporated by reference.

Alternatively, S-TOL can be prepared by stereoselective synthesis, using (other) chiral templates.

Alternatively, S-TOL can be obtained by the resolution of RS-TOL using conventional means such as fractional crystallization of diastereomeric salts with chiral acids. Other standard methods of resolution known to those skilled in the art, include, but are not limited to, crystallization and chromatography on a chiral substrate and can also be used.

The magnitude of a prophylactic or therapeutic dose of S-TOL in the acute or chronic management of disease will vary with the severity and nature of the condition to be treated and the route of administration. The dose and the frequency of the dosing will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for S-TOL for the conditions described herein is from about 0.5 mg to about 100 mg in single or divided doses, preferably in divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 0.5 mg to about 25 mg, and may be increased up to about 200 mg depending on the patient's global response.

It is further recommended that patients over 65 years and those with impaired renal or hepatic function initially receive low doses and that they be titrated based on individual response(s) and plasma drug level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat the disorder but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of S-TOL. For example, oral, sublingual, parental (i.e. subcutaneous, intramuscular, intravenous, etc.), transdermal, vaginal, aerosol and like forms of administration may be employed. Additionally, the drug may be administered directly into the bladder, as described for oxybutynin by Massad et al. [J. Urol. 148, 595-597 (1992)] or rectally directly into the gastrointestinal canal as known in the art. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, suppositories, microencapsulated systems, slowrelease and controlled release systems, transdermal delivery systems, and the like.

The pharmaceutical compositions of the present invention comprise of S-TOL as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, p-toluenesulfonic, succinic, sulfuric, tartaric, and the like. The hydrochloride is particularly preferred.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the more advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and delivery devices such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, and PCT application WO92/20377, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete unit dosage forms such as capsules, cachets, suppositories, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation, just as is known for the racemic mixture.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert

liquid diluent. All of the foregoing techniques are well know to persons of skill in the pharmaceutical art. Each tablet may contain from about 0.5 mg to about 25 mg of the active ingredient.

EXAMPLES

Example 1

ORAL UNIT DOSAGE FORMULATION

Tablets:

Ingredients	per tablet	per batch of 10,000 tablets
S-TOL	5 mg	50 g
Microcrystalline cellulose	30 mg	300 g
Lactose	70 mg	700 g
Calcium stearate	2 mg	20 g
FD&C Blue #1 Lake	0.03 mg	300 mg

The S-TOL is blended with lactose and cellulose until a uniform blend is formed. The lake is added and further blended. Finally, the calcium stearate is blended in, and the resulting mixture is compressed into tablets using a 9/32 inch (7 mm) shallow concave punch. Tablets of other strengths may be prepared by altering the ration of active ingredient to the excipients or to the final weight of the tablet.

Example 2.

Pharmacological Studies of S-TOL, RS-TOL or R-TOL

1. Ligand Binding Studies: Muscarinic Receptors.

The experimants are carried out on membranes prepared from SF9 cells infected with baculovirus to express human recombinant muscarinic receptor subtypes. After incubation with the test article and the proper radioligand and washing, bound radioactivity is determined with a liquid scintillation counter, using a commercial scintillation cocktail. The specific radioligand binding to each receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabelled ligand. IC_{50} values (concentrations required to inhibit 59% of specific binding) are determined by non linear regression analysis of the competition curves. These parameters are obtained by curve fitting using Sigmaplot™ software.

2. Functional Characterization of Antimuscarinic/Antispasmodic Activity.

Bladder and intestinal smooth muscle strips. Experiments are performed using methods similar to those described by Kachur et al, 1988 and Noronha-Blob and Kachur, 1991. Strips of tissue (approximately 10 mm long and 1.5 mm wide) are removed from the body of the urinary bladder of male Hartley guinea pigs weighing 400-600 g. Preparations of the longitudinal smooth muscle of the colon of guinea pigs are prepared as known in the art (Acta Physiol Scand 64: 15-27, 1965). The tissues are suspended in an oxygenated buffer of the following composition, in mM: NaCl, 133; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 0.6; NaH_2PO_4, 1.3; $NaHCO_3$, 16.3; and glucose, 7.7, or of a similar composition. They are maintained at 37.5 C. Contractions are recorded with isometric transducers (Model FT-10) on an ink-writing polygraph.

In each experiment up to seven strips are removed from a single animal, suspended in tissue chambers and allowed to equilibrate with the bathing solution for one hour before proceeding with the experiment.

Contractions induced by carbachol. One series of experiments focuses on the anticholinergic actions of S-TOL, RS-TOL or R-TOL. In these experiments, in order to assess the viability of each tissue and to serve as a frame of reference, contractions of each strip of tissue are recorded initially in response to exposure to tissue medium in which the NaCl was replaced by KCl to yield a concentration of 137.7 mM KCl in the medium. This is followed by return to the standard medium, and then by exposures to progressively in creasing concentrations of carbachol, with separate exposures to each concentration only until the peak response has been recorded. Then, leaving one strip untreated and/or one strip exposed to the test solution to serve as control tissue(s), the remaining strips each are exposed for one hour to one concentration of an antagonist. Finally, the responses to increasing concentrations of carbachol followed by exposure to 137.7 mM KCL are recorded a second time.

Contractions induced by hig potassium concentration. A second series of experiments focuses on the spasmolytic action of the substances being studied against high concentrations of K^+. Contractions in response to sequentially increasing the concentration of potassium in the medium are recorded.

Contractions induced by other spasmogens. A third series of experiments focuses on spasmolytic activities against other spasmogens. The contractions are recorded in response to sequentially increasing the concentration of such spasmogens in the medium.

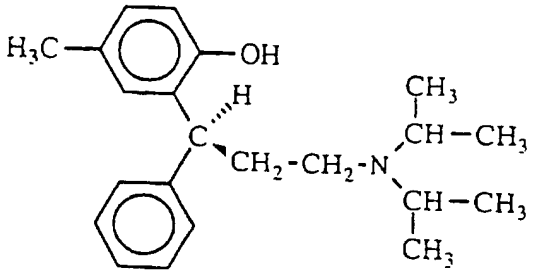
Data analysis. To determine whether antagonists decrease the peak response to agonists, the peak tension developed by each strip during the second set of determinations is expressed as a percent of the peak tension developed during the first concentration-effect determination. Then, for each antagonist the resultant data are analyzed for treatment-related differences by one-way analysis of variance (ANOVA). Since only one concentration of antagonist is studied in each strip of bladder, a modified procedure is used to estimate the pA2 and slope of the Schild regression. First, the concentrations of agonist producing a half-maximal response (the EC_{50}) is estimated for each strip from the second set of concentration-effect data. The EC_{50} is obtained from linear regression lines fit to the logarithm of the concentration of drug and the responses bracketing the half maximum level of response. For each drug-treated strip, a "concentration ratio" (CR) is calculated as the ratio of the EC_{50} of the treated tissue divided by the EC_{50} of the untreated tissue. For each experiment where two or more strips are exposed to the same chemical

but at different concentrations, the logarithm of this ratio minus one [i.e., log (CR-1)] is plotted against the logarithm of the concentration of antagonist to which the strip had been exposed to produce "Schild plots". A regression analysis relating log(CR-1) to the logarithm of the concentration of the antagonist is employed to estimate the pA2 and the slope of the regression line. Finally, experiments are grouped by chemical and the mean ± S.E.M. of the pA2 and slope are calculated.

Since S-TOL exhibits significantly decreased anticholinergic side effects as compared with the corresponding R-isomer and racemate, administration of S-tolterodine will allow avoidance of parasympathec cardiovascular side effects (i.e. tachycardia etc.) and other parasympathetic side effects (i.e. dry mouth, blurry vision, inhibition of normal urinary voiding mechanisms etc.), and the avoidance of memory loss that arise from the anticholinergic action of R-TOL. It is now therefore concluded that S-TOL is an effective medicament for the treatment of urinary voiding disorders, including urinary incontinence, and for the treatment of gastrointestinal disorders, including gastrointestinal hyperactivity in humans with greatly reduced side effects over the corresponding racemate or the pure R-enantiomer.

CLAIMS.

1. S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol. having the formula:



and pharmaceutically acceptable salts thereof.

2. A method for treating urinary voiding disorders , including incontinence, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol and pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

3. A method for treating gastrointestinal disorders. including gastro-intestinal hyperactivity, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol and pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

4. The method for treating urinary voiding disorders , including incontinence, while reducing concomitant liability of adverse effects associated with racemic tolterodine or the R-enantiomer of tolterodine, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salts thereof. substantially free of its R enantiomer.

5. The method for treating gastrointestinal disorders, including gastrointestinal hyperactivity, while reducing concomitant liability of adverse effects associated with racemic tolterodine or the R-enantiomer of tolterodine, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

6. The method of claim 4 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

7. The method of claim 5 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

8. The method of claim 4 wherein the amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered from about 0.5 mg to about 200 mg per day.

9. The method of claim 5 wherein the amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered from about 0.5 mg to about 200 mg per day.

10. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally.

11. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally.

12. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally in an extended release formulation.

13. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally in an extended release formulation.

14. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered transdermally.

15. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered transdermally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12155

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A 01 N 33/18
US CL : 514/741
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/741

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS
search terms: tolterodine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NILVEBRANT, L. Tolterodine--A New Baldder Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological Data. Life Sciences. 1977, Vol . 60, pages 1129-1136.	1-15
X	NILVEBRANT, L. Tolterodine-- A New Bladder Selective Antimuscarinic Agent. Eur. J. Pharmacol. 1977, Vol. 327, pages 195-207.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 11 SEPTEMBER 1997	Date of mailing of the international search report 24 SEP 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer GABRIELLE PHELAN Telephone No. (703) 308-2301

Form PCT/ISA/210 (second sheet)(July 1992)*

PATENT SPECIFICATION

624,117

Application Date: Dec. 7, 1946. No. 36257/46.

Complete Specification Left: Dec. 4, 1947.

Complete Specification Accepted: May 27, 1949.

Index at acceptance:—Class 2(iii), B4(a2: d), C2(a2: a14: b3), C3a13a3.

PROVISIONAL SPECIFICATION

Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

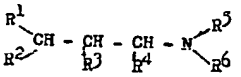
We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company), and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted propylamines which have valuable therapeutic properties.

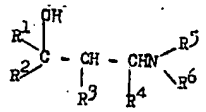
The object of our invention is to make possible the manufacture of certain novel substituted allylamines which are useful as starting materials for other production compounds.

A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

According to the process of our invention we make N-disubstituted-γγ-disubstituted allylamines of the formula

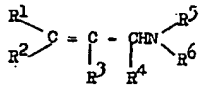


by the removal of the elements of water from the corresponding N-disubstituted-γγ-disubstituted-γ-hydroxy propylamines of the formula



In each of the general formulæ just given R^1 and R^2 are either identical or different and may be aryl, aralkyl or hydroaromatic groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino- or morpholino- groups.

According to a further feature of our invention, we convert the new substituted allylamines, described above, into N-disubstituted-γγ-disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent (e.g. petroleum ether).

Alternatively in some examples the base may be converted into a salt, particularly the hydrochloride, by treating the dried solution of the base in a solvent (for

example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

The manufacture of the N-disubstituted γγ-disubstituted-γ-hydroxy proplyamines used as starting materials is described in the specification of our co-pending application for Letters Patent No. 36258/46 (Serial No. 624,118) of even date herewith. Examples of such starting materials are γγ-diphenyl-γ-hydroxy-α-piperidinopropane and γγ-diphenyl-γ-hydroxy-α-dimethylaminopropane.

The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.

The manufacture by a different process of some of the N - substituted - γγ - disubstituted propylamines which may be made by the process of our invention has already been described, for example γγ-diphenyl - α - diethylamino - propane (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and γγ-diphenyl-α-piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma.

The invention is illustrated by the following example, in which quantities are given in parts by weight.

A solution of 15 parts γγ - diphenyl-γ-hydroxy - α - piperidinopropane hydrochloride in 30 parts concentrated aqueous hydrochloric acid and 100 parts glacial acetic acid was refluxed for 30 minutes. The solution kas then evaporated to dryness under reduced pressure and the residual solid dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ether solution was dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, γγ - diphenyl-α-piperidino-βγ-propylene, was collected as a colourless liquid, boiling point 138°C. at 0.1 mm. pressure.

Dry hydrogen chloride was passed through a solution of 10 parts of the base in 20 parts chloroform until acid to congo red and dry ether was added until crystallisation commenced. After standing for several hours the precipitate of γγ-diphenyl - α - piperidino - γ - propylene hydrochloride was filtered off and recrystallised from a mixture of chloroform and acetone. It had melting point 209—210°C.

A solution of 5 parts of the hydrochloride in 50 parts ethyl alcohol was shaken at room temperature (17°C.) with 0.1 parts of platinum oxide (prepared according to the directions given in Organic Syntheses, 1932, Collective, Volume 1, page 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen had been absorbed (after aproximately 3 hours) the catalyst was removed by filtration and the alcohol evaporated under reduced pressure. The solid residue was recrystallised from a mixture of alcohol and acetone when γγ - diphenyl - α - piperidinopropane hydrochloride was obtained as crystals, melting point 215—217°C.

Dated this 7th day of December, 1946.
G. H. FRAZER,
Chartered Patent Agent.

COMPLETE SPECIFICATION

Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company), and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

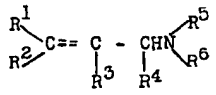
This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted propylamines which have valuable therapeutic properties.

The object of our invention is to make possible the manufacture of certain novel substituted allylamines which have valuable therapeutic activity and are also useful as starting materials for the production of other therapeutically valuable compounds.

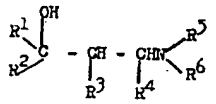
A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic

properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

According to the process of our invention we make N - disubstituted - γγ - disubstituted allylamines of the formula

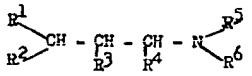


or salts thereof by the removal of the elements of water (by known methods for the conversion of tertiary alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted-γγ-disubstituted - γ - hydroxypropylamines of the formula



or salts thereof. In each of the general formulae just given R^1 and R^2 are aryl, aralkyl or cycloalkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^1 and R^2 may be identical, provided that both are not aralkyl groups; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino-, pyrrolidino- or morpholino- groups.

According to a further feature of our invention, we convert the new substituted allylamines, described above, or their salts, into N - disubstituted - γγ - disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

As a matter of scientific accuracy it may be mentioned that when R^1 or R^2 is an aralkyl or cycloalkyl group or when both R^1 and R^2 are cycloalkyl groups, the allylamine formed by the dehydration step is sometimes an isomer of the allylamine whose general formula is given above, the isomer differing from that of the said general formula only in the position of the double bond and the hydrogen atom. Or the product may be a mixture of such isomers. Both these isomers and mixtures thereof are to be regarded as lying within the scope of our invention, the general formula for these allylamines being read with the position of the double bond and hydrogen atom optional. Both the isomers, of course, yield identical N-disubstituted - γγ - disubstituted propylamines on reduction.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent wherein it is soluble (for example, petroleum ether).

Alternatively in some examples the base may be converted into its hydrochloride, by treating the dried solution of the base in a non-aqueous solvent (for example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

The manufacture of the N - disubstituted - γγ - disubstituted - γ - hydroxy propylamines used as starting materials is described in the Specification of our copending Application for Letters Patent, No. 36258/46 (Serial No. 624,118) of even date herewith. Examples of such starting materials are γγ - diphenyl - γ - hydroxy - α - piperidinopropane and γγ-diphenyl - γ - hydroxy - α - dimethylaminopropane.

The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.

The manufacture by a different process of some of the N substituted - γγ - disubstituted propylamines which may be made by the process of our invention has already been described, for example γγ - diphenyl-

α-diethylaminopropane (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and γγ-diphenyl-α-piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma. By research and experiment we have confirmed the correctness of this claim and have also demonstrated that the allylamines prepared in accordance with this invention likewise have valuable anti-spasmodic, anaesthetic and broncho-dilating activity.

The invention is illustrated by the following examples:—

EXAMPLE 1.

3 - N - Piperidino - 1:1 - diphenylpropan - 1 - ol hydrochloride (15 grams) is dissolved in a mixture of concentrated aqueous hydrochloric acid (30 cubic centimetres) and glacial acetic acid (100 c.c.s) and the solution boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure, the residual solid dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ether solution is dried over anhydrous sodium sulphate, the ether evaporated, and the residual oil distilled under reduced pressure, 3 - N-piperidino - 1:1 - diphenylprop - 1 - ene being collected as a colourles liquid, boiling point 138°C. at 0.1 millimetres pressure.

Dry hydrogen chloride is passed through a solution of the base (10 g.) in chloroform (20 c.c.s) until acid to congo red, and anhydrous ether is added until crystallisation commences. After standing for several hours, the precipitate of 3 - N - piperidino - 1:1 - diphenylprop-1 - ene hydrochloride is filtered off. After recrystallisation from a mixture of chloroform and acetone, the salt has melting point 209—210°C.

The hydrochloride (5 g.) is ethanol (50 c.c.s) is shaken at room temperature with platinum oxide (0.1 g., prepared according to the directions given in Organic Syntheses, 1932, Collective Volume 1, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the ethanol evaporated under reduced pressure. The crystalline residue is recrystallised from a mixture of ethanol and acetone, when 3 - N - piperidino - 1:1 - diphenylpropane hydrochloride is obtained, melting point 215—217°C. The base, liberated from the hydrochloride by treatment with aqueous alkali, has melting point 40—41°C.

EXAMPLE 2.

3 - Dimethylamino - 1:1 - diphenylpropan - 1 - ol (6.0 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 1, when 3 - dimethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, boiling point 192—3°C./18 mms. The hydrochloride prepared therefrom has melting point 168—170°C. (recrystallised from a mixture of ethanol and acetone).

3-Dimethylamino - 1:1 - diphenylprop-1 - ene (5.0 g.) is dissolved in ethanol (20 c.c.s.), 3% palladised charcoal (1.5 g.) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtrate by evaporation, and the residual oil fractionally distilled under reduced pressure. 3 - Dimethylamino-1:1-diphenylpropane distils at 183—185°C./16 mms., and crystallises on standing, melting point 44—45°C. (recrystallised from light petroleum).

EXAMPLE 3.

3-Diethylamino - 1:1 - diphenylpropan-1 - ol hydrochloride is dehydrated by the method described in Example 1. 3-Diethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 111°C./0.05 mms. The hydrochloride prepared therefrom has melting point 146—147°C. recrystallised from anhydrous acetone).

3 - Diethylamino - 1:1 - diphenylprop-1 - ene hydrochloride (6.0 g.) in ethanol (15 c.c.s) to which 3% palladised charcoal (2.0 g.) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino - 1:1 - diphenylpropane hydrochloride commences. The salt has melting point 145.5°C., and may be recrystallised from acetone.

EXAMPLE 4.

3 - N - Pyrrolidino - 1:1 - diphenylpropan - 1 - ol is dehydrated by the method described in Example 2. The product, 3-N-pyrrolidino - 1:1 - diphenylprop - 1-ene is obtained as a colourless oil, boiling point 125°C./0.02 mms., from which the hydrochloride, melting point 165—167°C. (recrystallised from a mixture of ethanol and ethyl acetate) is obtained.

The hydrochloride, when hydrogenated

by the method described in Example 3, yields 3-N-pyrrolidino - 1:1 - diphenylpropane hydrochloride of melting point 135—136°C. (recrystallised from a mixture of ethanol and ethyl acetate); the base obtained from the hydrochloride by treatment with aqueous alkali, has boiling point 125°C./0.02 mms.

EXAMPLE 5.

3-N-Morpholino - 1:1 - diphenylpropan - 1 - ol (6 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water and basified by addition of excess aqueous ammonia. The oil which separates crystallises on standing, and is removed by filtration and is washed with water. After crystallisation from ethanol, the product 3-N-morpholino - 1:1-diphenylprop-1-ene has melting point 70—72°C.; the hydrochloride prepared therefrom has melting point 218—219°C. (recrystallised from ethanol).

The hydrogenation of the hydrochloride, carried out using platinum oxide catalyst as described in Example 1 yields 3-N-morpholino - 1:1 - diphenylpropane hydrochloride, melting point 208—209°C. (recrystallised from a mixture of ethanol and ethyl acetate).

EXAMPLE 6.

Dehydration of 3-dimethylamino - 1:1-diphenylbutan - 1 - ol hydrochloride in a similar manner to that described in Example 1 yields 3-dimethylamino - 1:1-diphenylbut - 1 - ene, boiling point 194—196°C./19 mms., hydrochloride, melting point 160—161°C. (recrystallised from ethyl acetate). Hydrogenation is effected by shaking a solution of the hydrochloride (4.0 g.) in ethanol (20 c.c.s) with 3% palladised charcoal (2.0 g.) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3 - dimethylamino - 1:1 - diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176°C./12 mms. The hydrochloride obtained therefrom has melting point 157—158°C.

EXAMPLE 7.

3-Diethylamino - 1:1 - di - *p* - tolylpropan - 1 - ol hydrochloride is dehydrated by the method described in Example 1, when 3 - diethylamino - 1:1 - di - *p*-tolylprop - 1 - ene is obtained as a colourless liquid, boiling point 146—150°C./0.3 mms. pressure. The hydrochloride prepared from the base has melting point 179—180°C. (recrystallised from anhydrous acetone).

Hydrogenation of the hydrochloride by the method described in Example 3 yields 3 - diethylamino - 1:1 - di - *p*-tolylpropane hydrochloride, melting point 136—138°C. (recrystallised from ethyl acetate).

EXAMPLE 8.

3-Diethylamino - 1 - *cyclo*hexyl - 1 - phenylpropan - 1 - ol hydrochloride is dehydrated as described in Example 1, to give an unsaturated amine of boiling point 123—125°C./0.3 mms. pressure, from which the hydrochloride, melting point 157—160°C. (recrystallised from ethyl acetate) is obtained.

The hydrochloride when subjected to hydrogenation by the method described in Example 6, is converted into 3-diethylamino - 1 - *cyclo*hexyl - 1 - phenylpropane (boiling point 190—192°C./18 mms. pressure). The hydrochloride prepared therefrom has melting point 125—126°C. (recrystallised from ethyl acetate).

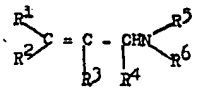
EXAMPLE 9.

Dehydration of 3 - diethylamino - 1-benzyl - 1 - phenylpropan - 1 - ol hydrochloride by the method described in Example 1 yields an unsaturated amine, which is obtained as a colourles oil on distillation under reduced pressure (boiling point 120—123°C./0.04 mms.). The hydrochloride obtained from the amine has melting point 157—159°C. after several recrystallisations from a mixture of ethanol and ethyl acetate.

Hydrogenation of the unsaturated amine by the method described in Example 2 yields 3 - diethylamino - 1-benzyl - 1 - phenylpropane, boiling point 112—114°C./0.02 mms. pressure, from which the hydrochloride, melting point 95—97°C. (recrystallised from ethyl acetate) is obtained.

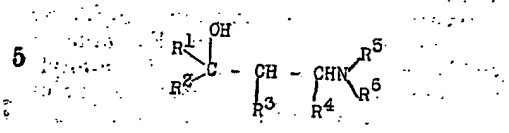
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the production of N-disubstituted - $\gamma\gamma$ - disubstituted allylamines of the formula



and salts thereof comprising the removal of the elements of water (by known methods for the conversion of tertiary

alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted - $\gamma\gamma$ - disubstituted - γ-hydroxy propylamines of the formula



in which the formulae R^1 and R^2 are aryl, aralkyl or cyclo-alkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^1 and R^2 may be identical, provided that both are not aralkyl groups; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino-, pyrrolidino- or morpholino- groups.

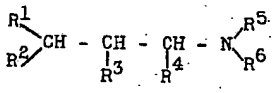
2. The process claimed in claim 1 wherein the substituted amino tertiary alcohol or a salt thereof is dissolved in a mixture of acetic acid and concentrated aqueous hydrochloric acid and the solution refluxed for a period of 15 minutes to one hour.

3. The process claimed in claim 1 or claim 2 wherein after dehydration of the tertiary alcohol the solution contained in the product is evaporated to dryness under reduced pressure, the residue is dissolved in water, excess of an alkali such as concentrated ammonia is added, and the liberated base is separated by extraction with an organic solvent such as ether.

4. The process claimed in claim 3 wherein the liberated base is recovered by evaporation of the solvent and distillation under reduced pressure or if the base is solid by recrystallisation from a solvent.

5. The process claimed in claim 3 wherein the base is converted into its hydrochloride by treating the dried solution of the base in a non-aqueous solvent with dry hydrogen chloride, thereby precipitating the base in the form of its hydrochloride and separating the latter from the solution.

6. The process claimed in claim 1 wherein the substituted allylamines prepared in accordance therewith are converted into N-disubstituted - $\gamma\gamma$ - disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

7. The process claimed in claim 6 wherein the reduction is carried out upon the base or its hydrochloride dissolved in water, ethyl alcohol or other solvent by the action of hydrogen in the presence of a hydrogenation catalyst.

8. The process claimed in claim 7 wherein the reduction is carried out at atmospheric pressure and the hydrogenation catalyst is platinum black or palladised charcoal.

9. The process of preparing N-disubstituted - $\gamma\gamma$ - disubstituted allylamines and N - disubstituted - $\gamma\gamma$ - disubstituted propylamines of the general formulæ hereinbefore given substantially as hereinbefore described in any of the Examples hereinbefore given.

10. N - disultituted - $\gamma\gamma$ - disubstituted allylamines and N - disubstituted - $\gamma\gamma$ - disubstituted propylamines having the general formulae hereinbefore given when prepared by the process claimed in any preceding claim.

Dated this 3rd day of December, 1947.
G. H. FRAZER,
Chartered Patent Agent.

Leamington Spa: Printed for His Majesty's Stationery Office, by the Courier Press.—1949.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies, price 2s. 0d. each (inland) 2s. 1d. (abroad) may be obtained.

PATENT SPECIFICATION

627,139

Application Date: May 28, 1947. No. 14160/47.

Complete Specification Left: May 7, 1948.

Complete Specification Accepted: July 29, 1949.

Index at acceptance: —Class 2(iii), B4(a2: a4: d), C2a(2: 14: 19), C2b(2: 3), C3a13a3.

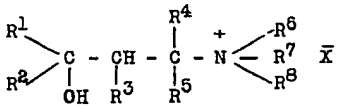
PROVISIONAL SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

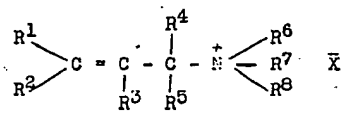
We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted-allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted - γ-hydroxypropylammonium salts, N-trisubstituted - γγ - disubstituted - allylammonium salts and N-trisubstituted-γγ-disubstituted-propylammonium salts of the general formula:—



(I)



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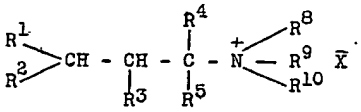


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

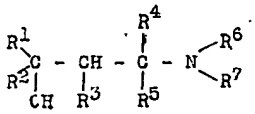
R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*-alkyl, aryl or aralkyl groups, or —NR^6R^7 may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or—NR^9R^{10} may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups,

$\bar{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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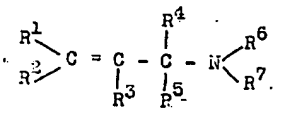

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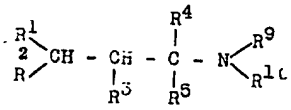


(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention, may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β-tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organomagnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted - allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ-hydroxy-propylamines of general formula (IIV (above). The N-disubstituted - $\gamma\gamma$ - disubstituted-propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents.

The following examples illustrate the invention:

EXAMPLE 1.

A solution of the ethyl ester of β-piperidinopropionic acid (37 parts by weight) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 2 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture which is cooled to 0° C., until acid to congo red. After standing for 1 hour at 0°C., the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 1:1-diphenyl-3-piperidinopropanol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropanol (1 part) is dissolved in anhydrous acetone (10 parts), methyl iodide (1 part) added and the mixture boiled under reflux for 15 minutes. On cooling N-methyl-3-hydroxy - 3:3 - diphenylpropylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C. (uncorrected).

EXAMPLE 2.

1:1-Diphenyl - 3 - dimethylaminopropanol is prepared from the ethyl ester of β - dimethylaminopropionic acid (29 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl - 3 - dimethylaminopropanol has melting point 167° C. (uncorrected) after recrystallisation from benzene or light petroleum.

1:1-Diphenyl - 3 - dimethylaminopropanol (4 parts) is dissolved in boiling ethyl alcohol (80 parts) and ethyl iodide (5 parts) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C. with decomposition (uncorrected) after recrystallisation from ethyl alcohol.

EXAMPLE 3.

1:1-Diphenyl - 3 - dimethylaminopropanol (2 parts) is dissolved in boiling ethyl alcohol (40 parts) and benzyl chloride (3 parts) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 parts) is gradually added, and the crystals of N-dimethyl-N-benzyl - 3 - hydroxy - 3:3 - diphenylpropylammonium chloride filtered off and recrystallised from ethyl alcohol; melting point 251° C. (uncorrected) with decomposition.

EXAMPLE 4.

1:1 - Diphenyl - 3 - diethylaminopropanol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1-Diphenyl-3-diethylaminopropanol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum has melting point 53° C. (uncorrected).

1:1 - Diphenyl - 3 - diethylaminopropanol (1 part) is dissolved in anhydrous acetone (2 parts), methyl iodide (1 part) in anhydrous acetone (2 parts) added and the mixture allowed to stand for 2 hours. N - Methyl-N-diethyl-3-hydroxy-3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C. (uncorrected).

EXAMPLE 5.

A solution of 1:1-diphenyl-3-piperidinopropanol (3 parts) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 parts) and glacial acetic acid (20 parts) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 1:1-diphenyl-3-piperidino-1:2-propene is collected as a colourless liquid, boiling point 138° C/0.1 mm. pressure.

1:1 - Diphenyl-3-piperidino-1:2-propene (1 part) is dissolved in anhydrous acetone (3 parts) and a solution of methyl iodide (1 part) in acetone (1 part) is added, when heat is developed. After standing for several hours, the crystals of N - methyl-3:3-diphenyl-allylpiperidinium iodide which separates are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C. (uncorrected) with decomposition.

EXAMPLE 6.

1:1-Diphenyl-3-piperidino - 1:2 - propene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C. (uncorrected).

1:1-Diphenyl-3-piperidino - 1:2 - propene hydrochloride (1 part) in ethyl alcohol (10 parts) is shaken at room temperature with platinum oxide (0.02 parts) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. I, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone, when 1:1 - diphenyl-3-piperidinopropane hydrochloric is obtained as crystals; melting point 215—217° C. (uncorrected). The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 1:1-diphenyl-3-piperidinopropane; melting point 39—40° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropane (1 part) is dissolved in anhydrous acetone (2 parts) and methyl iodide (1 part) in anhydrous acetone (1 part) is added. After standing for 2 hours the crystals of N - methyl - 3:3 - diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C. (uncorrected) with decomposition.

EXAMPLE 7.

1:1 - Diphenyl-3-diallylaminopropanol is prepared from the ethyl ester of β-diallylaminopropionic acid (39 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl-3-diallylaminopropanol has boiling point 157—159° C/0.4 mm. and melting point 25—27° C. (uncorrected) after recrystallisation from light petroleum (boiling point 40—60° C).

1:1 - Diphenyl - 3 - diallylaminopro-

panol (3 parts) is dissolved in anhydrous acetone (5 parts) and methyl iodide (2 parts) added to the solution. The fine needles of N - methyl - N - diallyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide which quickly separate, are recrystallised from aqueous ethyl alcohol; melting point 196—197° C. with decomposition (uncorrected).

EXAMPLE 8.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene is prepared from 1:1-diphenyl-3-diallylaminopropanol by dehydration by a method essentially similar to that described in Example 5 for the preparation of 1:1-diphenyl-3-piperidinol-:2-propene. 1:1-Diphenyl-3-diallylamino-1:2-propene is obtained as a colourless oil, boiling point 134° C/0.2 mm. by distillation under reduced pressure.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene (2 parts) is dissolved in anhydrous acetone (3 parts), methyl iodide (2 parts) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N - methyl-N-diallyl-3:3-diphenylallylammonium iodide are separated by filtration and recrystallised from ethyl alcohol; melting point 149—151° C. (uncorrected) with decomposition.

Dated this 28th day of May, 1947.

THE WELLCOME FOUNDATION LTD.,
A. N. FALDER,
Secretary.

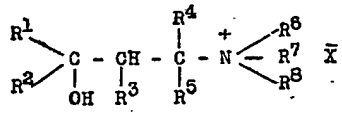
COMPLETE SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

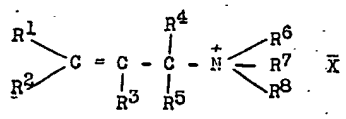
We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted-γ-hydroxypropylammonium salts and N-trisubstitued - γγ - disubstituted-propylammonium salts of the general formula:—



(I)



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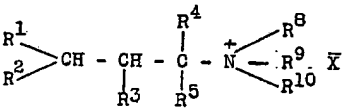


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

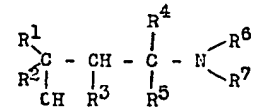
R^8 denotes an alkyl or aralkyl radical

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or $—NR^9R^{10}$

may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups, and

$\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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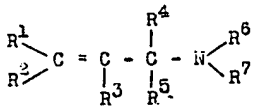
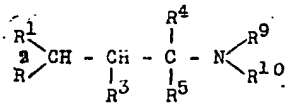


(V)

or



(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β - tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organo-magnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organiomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted-allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ - hydroxy - propylamines of general formula (IV) (above). The N-disubstituted - $\gamma\gamma$ - disubstituted - propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents having antispasmodic and broncho-dilating action.

The following examples illustrate the invention:—

EXAMPLE I.

A solution of the ethyl ester of β-piperidino-propionic acid (37 grams) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 cubic centimetres) and magnesium (17 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 2 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture, cooled to 0° C., until acid to congo red. After standing for 1 hour at 0° C. the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 3-N-piperidino-1:1-diphenylpropan-1-ol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C.

3 - N - Piperidino - 1:1 - diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (10 cubic centimetres), methyl iodide (1 gram) added and the mixture boiled under reflux for 15 minutes. On cooling N - methyl - 3-hydroxy-3:3-diphenyl - propylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C.

EXAMPLE 2.

A solution of 3 - piperidino - 1 : 1-diphenylpropan-1-ol (3 grams) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 cubic centimetres) and glacial acetic acid (20 cubic centimetres) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 3-N-piperidino-1 : 1-diphenylprop-1-ene, is collected as a colourless liquid, boiling point 138° C./at 0.1 mm. pressure.

3 - N-Piperidino-1 : 1-diphenylprop-1-ene (1 gram) is dissolved in anhydrous acetone (3 cubic centimetres) and a solution of methyl iodide (1 gram) in acetone (1 cubic centimetre) is added, when heat is developed. After standing for several hours, the crystals of N-methyl-3 : 3-diphenylprop - 2 - enylpiperidinium iodide which separate are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C., with decomposition.

EXAMPLE 3.

3 - N - Piperidino-1 : 1-diphenylprop-1-ene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C.

3-N-Piperidino - 1 : 1 - diphenylprop-1-ene hydrochloride (1 gram) in ethyl alcohol (10 cubic centimetres) is shaken at room temperature with platinum oxide (0.02 grams) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. 1, *p. 452*) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone when 3-N-piperidino-1 : 1-diphenylpropane hydrochloride is obtained as crystals, melting point 215—217° C. The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 3-N-piperidino-1 : 1-diphenylproprane, melting point 40—41° C.

3 - N - Piperidino - 1 : 1 - diphenylpropane (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres) and methyl iodide (1 gram) in anhydrous acetone (1 cubic centimetre) is added. After standing for 2 hours the crystals of N-methyl-3 : 3-diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C., with decomposition.

EXAMPLE 4.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol is prepared from the ethyl ester of β-dimethylaminopropionic acid (29 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N - piperidino-1 : 1-diphenylpropan-1-ol 3 - Dimethylamino-1 : 1-diphenylpropan-1-ol has melting point 166° C. after recrystallisation from benzene or light petroleum.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (4 grams) is dissolved in boiling ethyl alcohol (80 cubic centimetres) and ethyl iodide (5 grams) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy-3 : 3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C., with decomposition, after recrystallisation from ethyl alchohol.

EXAMPLE 5.

N - Dimethyl - N - propyl-3-hydroxy-3 : 3 - diphenylpropylammonium bromide similarly is prepared by boiling 3-dimethylamino - 1 : 1 - diphenylpropran-1-ol with 1-bromo-propane in ethanolic solution for 5 hours (under reflux). The product melts with decomposition at 231—233° C.

EXAMPLE 6.

N - Dimethyl-N-butyl-3-hydroxy-3 : 3-diphenylpropylammonium bromide is prepared from 3 - dimethylamino-1 : 1-diphenylpropan-1-ol and 1-bromobutane in a similar manner to that described in Example 5. It has melting point 233—235° C. (with decomposition).

EXAMPLE 7.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (2 grams) is dissolved in boiling ethyl alcohol (40 cubic centimetres) and benzyl chloride (3 grams) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 cubic centimetres) is gradually added and the crystals of N - dimethyl - N - benzyl-3-hydroxy - 3 : 3 - diphenylpropylammonium chloride filtered off and recrystal-

lised from ethyl alcohol; melting point 251° C., with decomposition.

EXAMPLE 8.

3-Dimethylamino - 1:1 - diphenylpropan-1-ol (6.0 grams) is dissolved in concentrated hydrochloric acid (18 cubic centimetres) and glacial acetic acid (60 cubic centimetres) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 2, when 3-dimethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, boiling point 102—3° C./18 mm.

The methiodide (N - trimethyl - 3:3-diphenylprop-2-enylammonium iodide) is prepared by the method described in Example 2. It melts with decomposition at 203—205° C., after recrystallisation from ethanol.

EXAMPLE 9.

3 - Dimethylamino-1:1-diphenylprop-1-ene (5.0 grams) is dissolved in ethanol (20 cubic centimetres), 3% palladised charcoal (1.5 grams) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtration by evaporation, and the residual oil fractionally distilled under reduced pressure. 3-Dimethylamino - 1:1 - diphenylpropane distils at 183—185° C./16 mm., and crystallises on standing, melting point 44—45° C. (recrystallised from light petroleum).

3-Dimethylamino - 1:1 - diphenylpropane (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. Heat is developed and crystals of N-trimethyl 2:3-diphenylpropylammonium iodide separate. The crystals are filtered off and recrystallised from a mixture of methanol and ethyl acetate; melting point 179—180° C.

EXAMPLE 10.

3 - Diethylamino-1:1-diphenylpropan-1-ol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N-piperidino - 1:1 - diphenylpropan - 1 - ol. 3-Diethylamino - 1:1 - diphenylpropan-1-ol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum, has melting point 53.5° C.

3 - Diethylamino-1:1-diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres), methyl iodide (1 gram) in anhydrous acetone (2 cubic centimetres) added, and the mixture allowed to stand for 2 hours. N-Methyl-N-diethyl - 3 - hydroxy - 3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C.

EXAMPLE 11.

3 - Diethylamino-1:1-diphenylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2. 3-Diethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 110° C./0.05 mm. The hydrochloride prepared therefrom has melting point 146—147° C. (recrystallised from anhydrous acetone).

The tertiary amine (3.0 grams) is dissolved in acetone (5.0 cubic centimetres) and methyl iodide (3.0 grams) in acetone (2 cubic centimetres) gradually added with cooling. The crystalline precipitate of N-methyl-N-diethyl - 3:3 - diphenylprop-2-enylammonium iodide is removed and recrystallised from methanol. It has a melting point of 185—186° C.

EXAMPLE 12.

3-Diethylamino - 1:1 - diphenylprop-1-ene hydrochloride (6.0 grams) in ethanol (15 cubic centimetres) to which 3% palladised charcoal (2.0 grams) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (after approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino-1:1-diphenylpropane hydrochloride commences. The salt has melting point 145.5° C. and may be recrystallised from acetone. The free base (obtained as a colourless liquid) is converted to the quaternary methiodide (N - methyl - N-diethyl - 3:3 - diphenylpropylammonium iodide) of melting point 162—163° C. (recrystallised from aqueous ethanol) by the method described in Example 2.

EXAMPLE 13.

Ethyl β - di-*n*-propylaminopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume 67, page 1071) (40.2 grams) in anhydrous ether (50 cubic centimetres) treated with the Grignard reagent made from bromobenzene ((110 grams) and magnesium (17 grams) under the conditions described in Example 1, yields 3-di-*n*-propylamino - 1:1 - diphenylpropan-1-ol which is purified by fractional distillation under reduced pressure (boiling point 153—154° C. at 0.1 mm.) and by recrystallisation from light petroleum; the base has melting point 52.5—53.5° C.

The methiodide (N-methyl-N-dipropyl-3:3-diphenyl - 3 - hydroxypropylammo-

nium iodide) prepared therefrom by the method described in Example 2 has melting point 181—183° C., after recrystallisation from aqueous ethanol.

EXAMPLE 14.

Ethyl β-N-phenyl-N-methylaminopropionate (41.4 grams) in ether (100 cubic centimetres), treated with the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) in ether (200 cubic centimetres) in a similar manner to that described in Example 1, yields 3-N-phenyl-N methylamino-1:1-diphenylpropan-1-ol, melting point 97° C. (recrystallised from ethanol). The ethyl β-N-phenyl - N - methylaminopropionate used as starting material is prepared by a method essentially similar to that described by Elderfield, Gensler, Bembry, Kremer, Brody, Hageman and Head, *Journal of the American Chemical Society*, 1946, Volume *68*, page 1259, for the preparation of β-arylaminopropionic esters.

A mixture of ethyl acrylate (40g.), methylaniline (42.8 grams) and acetic acid (10 grams) is boiled under reflux for 12 hours, cooled, and taken up in an equal volume of ether. The ethereal solution is then washed with water, then with aqueous sodium bicarbonate solution and finally with water. The ethereal solution is then dried with anhydrous sodium sulphate, the ether evaporated, and the residual oil fractionally distilled under reduced pressure. The required ester is collected at 98—100° C/0.05 mm.

3-N-Phenyl - N - methylamino - 1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in ethanol (5.0 c.c.), methyl iodide (2.0 grams) added and the mixture allowed to stand for 24 hours. The N-dimethyl-N-phenyl - 3:3 - diphenyl-3-hydroxypropylammonium iodide which separates melts with decomposition at 176° C., after recrystallisation from aqueous ethanol.

EXAMPLE 15.

Ethyl - β - N - methyl-N-β-phenylisopropylaminopropionate (49.8 grams) in ether (100 cubic centimetres) is added dropwise to an ethereal solution of the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) and the mixture boiled under reflux for 2 hours. The cooled mixture is then poured on to crushed ice (100 grams) and acidified to congo red by the gradual addition of hydrochloric acid (concentrated). A gum, which rapidly solidifies, is precipitated, separated by filtration and washed with ether. The solid is then suspended in water (100 cubic centimetres) and chloroform (100 cubic centimetres) excess aqueous ammonia added with shaking, and the chloroform layer separated and dried over anhydrous sodium sulphate. Dry hydrogen chloride is then passed into the filtered chloroform solution until acid to congo red and other added to the point of crystallisation. 3-N-Methyl-N-2'-phenyl-1'-methylethylamino - 1:1 - diphenylpropan-1-ol hydrochloride separates and has melting point 207—208° C. after recrystallisation from aqueous ethanol; the base, liberated from the hydrochloride by addition of aqueous alkali, is a viscous oil.

The ethyl-β-N-methyl-N-β-phenyl*iso*propylminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenylisopropylaminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenyl*iso*propylmethylamine (60 grams) to stand for 48 hours, then boiling under reflux for 4 hours and subsequently fractionally distilling the product under reduced pressure (boiling point 165—166° C./12 mm.).

The methiodide of the base is prepared by mixing with methyl iodide in acetone solution as described in Example 2. The product melts with decomposition at 226° C.

EXAMPLE 16.

Ethyl β-N-pyrolidinopropionate when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-pyrrolidino-1:1-diphenyl-propan-1-ol melting point 171—172° C. (recrystallised from ethyl acetate).

The ethyl β-N-pyrrolidinopropionate is prepared by mixing pyrrolidine (21 grams) with ethyl acrylate (30 grams) and allowing to stand at room temperature for several days. The product is distilled under reduced pressure, the required ester being collected at 108—110° C./23 mm.

3 - N - Pyrrolidino-1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in chloroform (25 cubic centimetres), methyl iodide (2.0 grams) added, and the mixture allowed to stand for 24 hours. The crystals of N-methyl-3:3-diphenyl-3-hydroxypropylpyrrolidinium iodide which separate are recrystallised from methanol; melting point 210° C.

EXAMPLE 17.

Ethyl β-N-morpholinopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume *67*, page 1071,) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-

morpholino-1:1-dihpenylpropan - 1 - ol melting point 106° C. (recrystallised from light petroleum).

The corresponding methiodide is prepared by the method described in Example 1; it melts with decomposition at 203—204° C.

EXAMPLE 18.

3 - Diallylamino-1:1-diphenylpropan-1-ol is prepared from ethyl β-diallylaminopropionate (39 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 for the preparation of 3-N-piperidino-1:1-diphenyl-propan-1-ol. The product has boiling point 157—159° C./0.4 mm. after recrystallisation from light petroleum.

3 - Diallylamino-1:1-diphenylpropan-1-ol (3 grams) is dissolved in anhydrous acetone (5 cubic centimetres) and methiodide (2 grams) added to the solution. The fine needles of N-methyl-N-diallyl-3:3 - diphenyl-3-hydroxypropyl - ammonium iodide which quickly separate are recrystallised from aqueous methyl alcohol; melting point 196—197° C., with decomposition.

EXAMPLE 19.

3 - Diallylamino-1:1-diphenylprop-1-ene is prepared from 3-diallylamino-1:1-diphenylpropan-1-ol by dehydration by a method essentially similar to that described in Example 2 for the preparation of 3-piperidino-1:1-diphenyl-prop-1-ene. The product is a colourless oil, of boiling point 134° C./0.2 mm.

3 - Diallylamino-1:1-diphenylprop-1-ene (2 grams) is dissolved in anhydrous acetone (3 cubic centimetres), methyl iodide (2 grams) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N-methyl-N-diallyl-3:3-diphenylprop-2-enylammonium iodide are separated by filtration and recrystallised from ethanol, melting point 149—151° C. with decomposition.

EXAMPLE 20.

Ethyl β-dimethylaminobutyrate (prepared as described by Breckpot, Bulletin Societe Chimique de Belgique 1923, volume *32*, page 412) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-dimethylamino - 1:1-diphenyl-butan-1-ol melting point 125—126° C. (recrystallised from aqueous ethanol). The tertiary amine (2.0 grams) is dissolved in warm acetone (10 cubic centimetres), methyl iodide (2.0 grams) added and the mixture boiled under reflux for 15 minutes. On cooling and standing, the corresponding morpholino-1:1-diphenylpropan - 1 - ol ing point 251° C. after recrystallisation from aqueous ethanol.

EXAMPLE 21.

Dehydration of 3-dimethylamino-1:1-diphenylbutan-1-ol hydrochloride in a similar manner to that described in Example 2 yields 3-dimethylamino-1:1-diphenylbut-1-ene, boiling point 194—196° C./19 mm., (hydrochloride, melting point 160—161° C.)

The methiodide prepared therefrom by the method described in Example 2 melts with decomposition at 210—212° C. after recrystallisation from aqueous ethanol.

EXAMPLE 22.

Hydrogenation of 3-dimethylamino-1:1-diphenylbut-1-ene hydrochloride (4.0 grams) is effected by shaking in ethanol (20 cubic centimetres) with 3% palladised charcoal (2.0 grams) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3-dimethylamino-1:1-diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176° C./12 mm.

The methiodide prepared therefrom by the method described in Example 2 has melting point 204—205° C. after recrystallisation from ethanol.

EXAMPLE 23.

Ethyl β - diethylaminopropionate (26 grams) in anhydrous ether (50 c.c.) is added dropwise to an ether solution of the Grignard reagent made from *p*-bromotoluene (90 grams) and magnesium (12.8 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour and boiling under reflux for 2 hours, the reaction mixture is worked up as described in Example 1. The 3-diethylamino-1:1-di - *p* - tolylpropan - 1 - ol so obtained is purified by fractional distillation under reduced presure (boiling point 160—162° C./0.5 mm.) and may be recrystallised from a small volume of light petroleum, melting point 56—58° C.

The methiodide prepared therefrom (method described in Example 2) has melting point 188—189° C. (may be recrystallised from aqueous ethanol).

EXAMPLE 24.

3 - Diethylamino-1:1-di-*p*-tolylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2, when 3-diethylamino-1:1-di-*p*-tolylprop-1-ene is obtained as a colourless liquid, boiling point 146—150° C./0.3 mm. pressure.

The tertiary base (1.5 grams) in methanol (3 cubic centimetres) is mixed with methyl iodide (1.5 grams) when heat is developed. After standing for several hours, anhydrous ether is added dropwise with stirring until precipitation of the methiodide is complete. N-Methyl-N-diethyl-3:3-di-*p*-tolylprop-2-enyl-ammonium iodide melts with decomposition at 141—143° C. after recrystallisation from a mixture of ethyl acetate and ethanol.

EXAMPLE 25.

3-Diethylamino-1:1-di-*p*-tolylprop-1-ene hydrochloride (melting point 179—180° C.; which was obtained from the base described in Example 24) when hydrogenated by the method described in Example 3, yields 3-diethylamino-1:1-di-*p*-tolylpropane hydrochloride, melting point 136—138° C. (recrystallised from methyl acetate) from which the base is obtained as an oil.

The methiodide prepared from the tertiary amine, as described in Example 2, has melting point 169—170° C. after recrystallisation from ethanol.

EXAMPLE 26.

β-Diethylaminopropiophenone hydrochloride (prepared as described by Blicke and Burckhalter, *Journal of the American Chemical Society*, 1942, Volume *64*, page 451) (48.3 grams) is added in small portions to the Grignard reagent prepared from benzyl chloride (76 grams) and magnesium (14.6 grams) in ether (100 cubic centimetres), stirred and cooled to 0° C. The reaction and working up of the product is then carried out as described in Example 1. 4-Diethylamino-1:2-diphenylbutan-2-ol is obtained as crystals, melting point 54—55° C. (recrystallised from light petroleum).

The methiodide prepared therefrom by the method described in Example 2, has melting point 197—198° C. after recrystallisation from methanol.

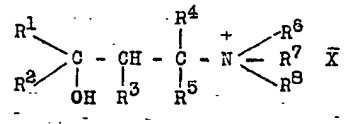
EXAMPLE 27.

β-Diethylaminopropionphenone hydrochloride (48.3 grams) is added in small portions to the Grignard reagent prepared from *cyclo*hexyl bromide (98 grams) and magnesium (14.6 grams) in 100 c.c ether stirred and cooled to 0° C. After boiling under reflux for 12 hours the product is worked up by a similar method to that described in Example 1. 3-Diethylamino-1-*cyclo*hexyl-1-phenylpropan-1-ol is purified by distillation under reduced pressure (boiling point 132—135° C./0.02 mm.) and by recrystallisation from light petroleum (melting point 50.5—52° C.).

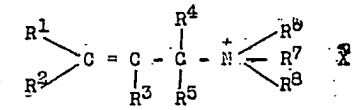
The tertiary base (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. After standing for several hours, crystallisation of the product is completed by gradual addition of anhydrous ether N-Methyl-N-diethyl-3-*cyclo*hexyl-3-phenyl-3-hydroxypropylammonium iodide has melting point 160—162° C. after recrystallisation from ethyl acetate and ethanol.

Having now particularly described and ascertained the nature of our said invention, and in what manner the same is to be performed, we declare that what we claim is:—

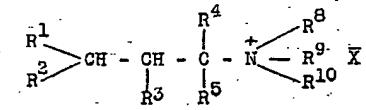
1. A process for the preparation of N-trisubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylammonium salts, N-trisubstituted-$\gamma\gamma$-disubstituted-allylammonium salts and N-trisubstituted-$\gamma\gamma$-disubstituted-propylammonium salts of the general formula:—



(I)



(II)



(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical,

R^4 denotes hydrogen or an alkyl radical,

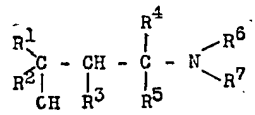
R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical.

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $-NR^6R^7$ may denote the pyrrolidino-, morpholino, or piperidino-group, optionally substituted by one or more alkyl groups,

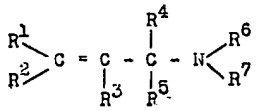
R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or $-NR^9R^{10}$ may denote the pyrrolidino-, morpho-

lino-, or piperidino-group, optionally substituted by one or more alkyl groups, and $\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical, comprising treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



(IV)



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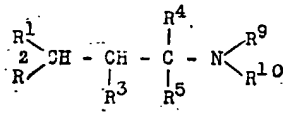

(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6 R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

2. The process claimed in claim 1 in which an excess of the reactive acid salt R^8X is present during the reaction.

3. The process claimed in claim 1 in which a solvent for both reactants is present during the reaction and the reaction is carried out at room temperature or at the boiling point of the solvent or at some intermediate temperature.

4. The process claimed in claim 3 in which the solvent is so selected and is present in such quantity that the desired quaternary salt crystallizes from the reaction mixture on cooling the latter.

5. The process claimed in claim 3 in which a liquid in which the reaction product is insoluble is added gradually to the reaction mixture after the reaction has been completed, until crystallization of the reaction product occurs.

6. The process claimed in claim 3 in which the solvent employed is anhydrous acetone, ethyl alcohol or dioxan.

7. A process for preparing compounds having the general formulae I, II or III given in claim 1, substantially as hereinbefore described.

8. A process for preparing a chemical compound having a formula within the scope of the general formulae I, II or III given in claim 1, substantially as described in any one of the Examples hereinbefore given.

9. A chemical compound when prepared by the process claimed in any preceding claim.

Dated this 7th day of May, 1948.

THE WELLCOME FOUNDATION LTD.,
A. N. FALDER,
Secretary.

Leamington Spa: Printed for His Majesty's Stationery Office, by the Courier Press.—1949.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies, price 2s. 0d. each (inland) 2s. 1d. (abroad) may be obtained.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 667 852 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
08.04.1998 Bulletin 1998/15

(21) Application number: **93924876.1**

(22) Date of filing: **05.11.1993**

(51) Int Cl.[6]: **C07C 217/62**, C07C 215/54, C07C 311/37, C07C 237/30, C07D 295/06, C07D 211/14, C07D 207/06, A61K 31/135

(86) International application number:
PCT/SE93/00927

(87) International publication number:
WO 94/11337 (26.05.1994 Gazette 1994/12)

(54) NOVEL 3,3-DIPHENYLPROPYLAMINES, THEIR USE AND PREPARATION

3,3-DIPHENYLPROPYLAMINE, IHRE VERWENDUNG UND HERSTELLUNG

NOUVELLES 3,3-DIPHENYLPROPYLAMINES, LEUR UTILISATION ET LEUR PREPARATION

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **06.11.1992 SE 9203318**

(43) Date of publication of application:
23.08.1995 Bulletin 1995/34

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(56) References cited:
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DE-B- 1 216 318
GB-A- 1 169 944
GB-A- 1 169 945

EP 0 667 852 B1

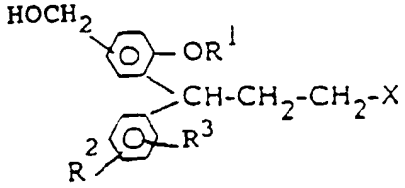
Printed by Jouve, 75001 PARIS (FR)

Description

The present invention relates to novel therapeutically active compounds, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

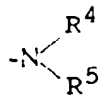
WO 89/06644 discloses 3,3-diphenylpropylamines having anticholinergic activity. In accordance with the present invention novel therapeutically active compounds have now been found, some of which are formed as metabolites in mammals when treated with the 3,3-diphenylpropylamines disclosed in the above-mentioned WO publication. These metabolites have at least as favourable anti-cholinergic properties as the parent compounds and can thus be used for the control of events mediated by acetylcholine, like urination.

The novel compounds of the present invention are represented by the general formula I



I

wherein R^1 signifies hydrogen or methyl, R^2 and R^3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



II

wherein R^4 and R^5 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and wherein R^4 and R^5 may form a ring together with the amine nitrogen, said ring having no other heteroatom than the amine nitrogen.

The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

In the compounds of formula I, R^2 is preferably hydrogen, and R^3 is preferably hydrogen or hydroxy.

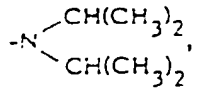
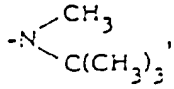
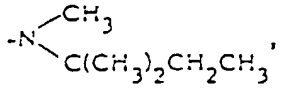
R^2 is preferably in 3-, 4- or 5-position.

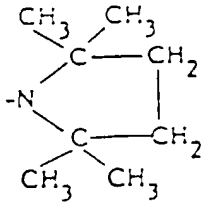
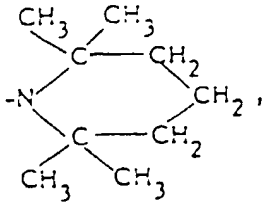
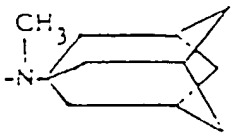
R^3 is preferably in 2-position with respect to the propylamine group.

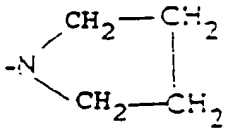
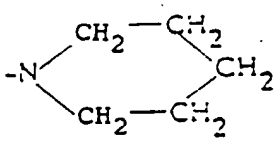
The $HOCH_2$-group is preferably in 5-position.

Preferably, each of R^4 and R^5 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably at least four carbon atoms. R^4 and R^5 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino groups X in formula I include the following groups a) - h):

a)  , b)  , c) 

d)  , e)  , f) 

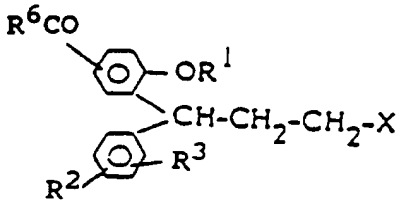
g)  , h) 

Preferably, R^4 and R^5 are both isopropyl.

A presently preferred specific compound of formula I is N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine.

The compounds of formula I may, in accordance with the present invention, be prepared by per se conventional methods, and especially by

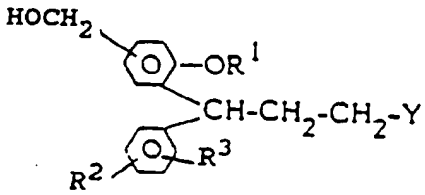
a) reducing the group R^6CO in a 3,3-diphenylpropylamine of formula III



III

wherein R^1 to R^3 and X are as defined above, R^6 is hydrogen or R^7O, where R^7 is hydrogen, (preferably lower) alkyl, alkenyl, alkynyl or aryl (such as phenyl) and any hydroxy groups may be protected, such as by methylation or benzylation, or

b) reacting a reactively esterified 3,3-diphenylpropanol of formula IV



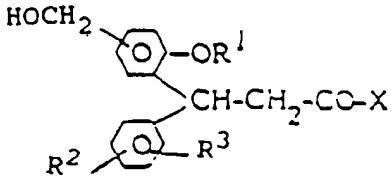
IV

wherein R^1 to R^3 are as defined above and any hydroxy groups may be protected, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group, with an amine of formula V

H - X V

wherein X is as defined above, or

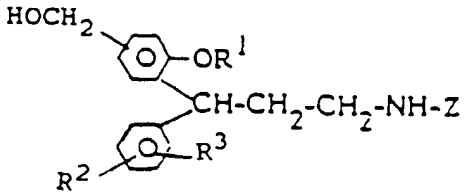
c) reducing a 3,3-diphenylpropionamide of formula VI



VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride, or

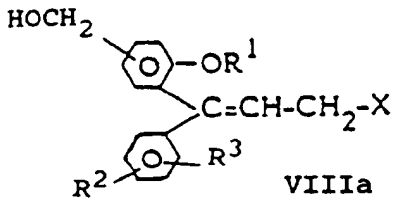
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



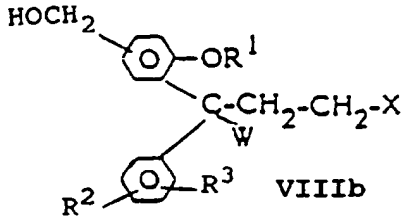
VII

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^4 and R^5 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

e) reducing a 3,3-diphenylpropenamine of formula VIIIa or a 3,3-diphenylpropylamine of formula VIIIb



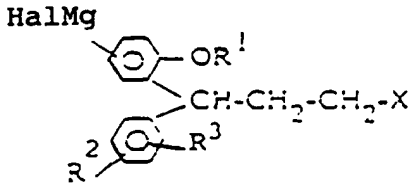
VIIIa



VIIIb

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, preferably by means of catalytic hydrogenation,

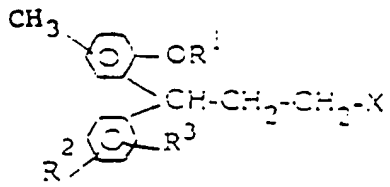
f) reacting a 3,3-diphenylpropylamine of formula IX



IX

wherein R^1 to R^3 and X are as defined above, and Hal is halogen, with formaldehyde or a formaldehyde equivalent (such as s-trioxane), or

g) oxidizing the methyl group of a diphenylpropylamine of formula X



X

wherein R^1 to R^3 and X are as defined above, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono- or di-halogenation of one or both of the phenyl rings, and/or

ii) if desired converting the obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or

iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^3 is hydroxy.

The oxidation in process g) above may be performed chemically, electrochemically or enzymatically. Chemical oxidation is advantageously performed using a metal salt or oxide like ceric ammonium nitrate, manganese oxides, chromium oxides, vanadinium oxides, cobalt acetate, aluminium oxide, bismuth molybdate or combinations thereof. Chemical oxidation may also be effected by peracids, with or without a catalyst, or with halides. Electrochemical oxidation may be conducted with or without a catalyst. For enzymatical oxidation, it is preferred to use bacteria or yeast (e.g. Candida Guilliermondi, Candida Tropical is).

The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

The starting compounds of formula III and IX may be prepared as described in the preparation example described below. The starting materials used in processes b) to e) and g) may be prepared as described in the afore-mentioned WO 89/06644 (the disclosure of which is incorporated by reference herein) with due consideration of the disclosure in the present preparation example.

In accordance with the present invention, the compounds of formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions can, as mentioned above, be used for the same therapeutical indications as the compounds of the above-mentioned WO 89/06644, i.e. for the treatment of acetylcholine-mediated disorders, such as urinary incontinence. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kilo of body weight, administered singly or multiply in doses e. g. from about 0,05 mg to about 200 mg each.

The invention will be further illustrated by the following non-limiting example and pharmacological tests. Reference will be made to the accompanying drawing where the only figure (Fig. 1) shows bladder pressure inhibition curves for a compound of the present invention and a prior art compound, respectively.

General

N.M.R data were acquired on a Jeol JNM-EX 270 Fourier transform spectrometer. Spectra were recorded with tetramethylsilane (TMS) as internal standard at 30°C. Infrared spectra were recorded on a Perkin Elmer 599B instrument. Non-corrected melting points were obtained on a Koeffler apparatus. Gas chromatography was performed on a HP 5940 instrument with a 10 m HP-1 column and the oven heated in the linear temperature gradient mode.

EXAMPLE 1

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine (+) mandelate, and (-)-N N-diisopropyl-3-(2-hydroxy-5-hvdroxymethylphenyl)-3-phenylpropylamine (-) mandelate

a) 6-Bromo-4-phenyl-3,4-dihydro-coumarine

A solution of p-bromophenol (138 g, 0.8 mole), cinnamic acid (148 g, 1.0 mole), acetic acid (200 g) and conc. sulfuric acid was refluxed for 2 h. Volatile material was distilled at reduced pressure. The residual syrup was cooled and triturated with cold water, giving a semi-crystalline mass. This was washed extensively with water, saturated sodium carbonate and finally with water again. The material was filtered through a sintered glass funnel, and then mixed with an equal weight of ethanol. The slurry was stirred at room temperature for 1 h and then filtered. The resulting product was washed briefly with ethanol and then diisopropyl ether. After drying, 135 g (55.7%) of the title compound was isolated as white crystals, melting at 117°C.

b) Methyl 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanonate

6-Bromo-4-phenyl-3,4-dihydro-coumarine (290 g, 0.96 mole) was dissolved in a mixture of methanol (1 L) and acetone (1 L). To the above solution were added potassium carbonate (160 g, 1.16 mole), α-chlorotoluene (140 g, 1.1 mole) and sodium iodide (30 g, 0.47 mole), and the mixture was stirred under reflux for 3 h. The solution was concentrated by distillation, and the residue treated with water and extracted with diethyl ether. The ethereal layer was washed with water, saturated sodium carbonate solution and water, successively. The organic layer was dried over sodium sulfate, filtered and then evaporated to give 420 g (≈100%) of the title compound as a light yellow oil.

c) 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanol

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanonate (112 g, 0.26 mole) was dissolved in tetrahydrofuran (250 mL) and added dropwise under nitrogen atmosphere to a suspension of lithium aluminiumhydride (5.9 g, 0.16 mole) in tetrahydrofuran (250 mL). The mixture was stirred overnight under nitrogen atmosphere. The excess hydride was decomposed by addition of a small amount of HCl (aq, 2 M). The solution was filtered on a pad of Celatom, and the solids were washed thoroughly with ether. The combined ethereal solution was washed with HCl (2 M), water, sodium hydroxide (2 M) and then with water again. The organic solution was dried over sodium sulfate, filtered and evaporated to give 98.5 g (95%) of the title compound as a colourless oil. A small fraction of the oil was crystallized from diisopropyl ether/petroleum ether giving crystals which melted at 70°C.

d) 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate

To a solution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanol (107 g, 0.24 mole) in dichloromethane (300 mL) and pyridine (75 mL) at 0°C was added p-toluene sulfonylchloride (57 g, 0.3 mole). The solution was stirred at 0°C overnight and then evaporated at reduced pressure and at a bath temperature below 50°C. The remainder was poured onto water and then the mixture was extracted with diethyl ether. The organic layer was washed with water, HCl (2 M) and water successively, and finally dried over sodium sulfate. After filtration the ethereal solution was evaporated at a bath temperature of <50°C giving 137 g (≈100%) of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate as a pale yellow oil.

e) N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine

3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate (115 g, 0.2 mole) was dissolved in a mixture of acetonitrile (150 g) and diisopropylamine (202 g, 2.0 mole) and the mixture was refluxed for 4 days. The solution was evaporated, and to the resulting syrup was added sodium hydroxide (2 M, 200 mL). The mixture was concentrated, cooled and then extracted with diethyl ether. The ethereal layer was extensively washed with water. The amine was extracted with excess sulfuric acid (1 M). The aqueous layer was washed with diethyl ether and then basified with sodium hydroxide (11 M). The mixture was then extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered and then evaporated to give 78.6 g (78%) of N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine as a pale yellow oil. The 1-H N.M.R spectrum was in accordance with the above structure.

f) Resolution

To a solution of N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine (255 g, 0.53 mole) in ethanol (750 g) was added L-(+)-tartaric acid (80 g, 0.53 mole). When all material was dissolved, diethyl ether (90

g) was added and crystallization commenced. After being stored at room temperature overnight, the formed salts were filtered off, washed with fresh ethanol-diethyl ether solution (2:1) and dried to give 98 g of white crystals melting at 156°C. $[\alpha]^{22}$= 16.3° (c = 5.1, ethanol)

The mother liquor from the precipitation with L-(+)-tartaric acid was evaporated. The resulting syrup was treated with sodium hydroxide (2 M) and extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and then evaporated, giving 170 g of free base. The base (170 g, 0.35 mole) was dissolved in ethanol (500 mL), and D-(-)-tartaric acid (53 g, 0.53 mole) was added. When all had dissolved, diethyl ether (50 mL) was added and crystallization commenced. The crystals were filtered off and washed with fresh ethanol-diethyl ether solution giving 105 g of crystals melting at 154-155°C. $[\alpha]^{22}$ = -16.4° (c = 5.0, methanol)

The mother liquor was concentrated, basified and treated as above, yielding 80 g of free base. This base was dissolved in ethanol, and treated with L-(+)-tartaric acid as described above, yielding additional 20 g of the dextrorotatory form of the salt. (M.p. 156°C).

In an analogous manner, 20 g of the levorotatory form could be obtained.

The pooled dextrorotatory form was dissolved in water and basified with sodium hydroxide (2 M). The mixture was then extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and finally evaporated to give the chiral amine (88 g) as a colourless oil. $[\alpha]^{22}$ = 16.3° (c = 5.1, ethanol)

In an analogous fashion, the levorotatory base was obtained (90 g). $[\alpha]^{22}$ = -16.1° (c = 4.2, ethanol). The optical purity as assessed by chromatography was >99%.

g1) (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine hydrochloride

A mixture of magnesium (12.2 g, 0.5 mole), ethyl bromide (2 g), and iodine (a small crystal) in dry diethyl ether (200 mL) was warmed until the reaction started. (+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine (45.6 g, 0.095 mole) and ethyl bromide (32.7 g, 0.3 mole) dissolved in dry diethyl ether (250 mL) were then added dropwise under nitrogen atmosphere. The mixture was refluxed for 1.5 h and then cooled in an acetone/dry-ice bath, whereupon powdered dry ice (≈100 g) was added gently. Tetrahydrofuran was added when needed to prevent the mixture from solidification. The reaction mixture was stirred for 0.5 h when ammonium chloride (200 mL, 20% w/w) was added. The mixture was stirred vigorously until two transparent phases were formed, and then filtered through a pad of Celatom. The aqueous layer was washed with diethyl ether and then acidified with hydrochloric acid to pH 1. The precipitated semi-crystalline gum was washed with water, and then transferred to a round bottom flask. The product was dried by co-evaporation with acetone, benzene, toluene, diisopropyl ether and methanol, successively. The title compound (35.1 g, 77%) was isolated as friable shiny flakes and used without any further purification.

g2) (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine hydrochloride

This product was isolated in 81 % yield in a corresponding way as described above from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine.

h1) (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl-3-phenylpropylamine

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine (34 g, 0.07 mole) was dissolved in methanol (300 mL) containing sulfuric acid (6 g) and refluxed for 6 h. The solution was then cooled and concentrated. To the mixture were added ice-water and a slight excess of saturated sodium carbonate solution. The mixture was then extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and evaporated, giving 30 g (93%) of crude ester. Recrystallisation from diisopropyl ether gave white crystals melting at 85-86°C. The 1-H N.M.R. spectrum was in accordance with the above structure.

h2) (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine

The title compound was obtained from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine in a similar manner as described above for the dextro isomer in a 93 % yield.

i1) (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine (30 g, 0.065 mole) dissolved in diethyl ether (250 mL) was added dropwise under nitrogen to a suspension of lithium aluminiumhydride (1.9 g, 0.05 mole) in dry diethyl ether (150 mL). The mixture was stirred overnight at room temperature, and the excess hydride was decomposed by the addition of water (≈5 g). The mixture was stirred for 10 min, when sodium sulfate (s) was added. After stirring for 20 minutes, the mixture was filtered and then evaporated to give 28.4 g of the title compound as a colourless oil.

i2) (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine

The title compound was obtained in an analogous fashion as described above for the levo isomer from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine.

j1) (+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium (+) mandelate

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine (28.2 g, 0.065 mole) was dissolved in methanol (300 g). Raney Nickel (one teaspoon) was added and the mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen was consumed. The progress of the reaction was

monitored by gas chromatography. The mixture was then filtered through a pad of Celatom, and the solvent was removed by evaporation at a bath temperature <50°C. The resulting oil was dissolved in diethyl ether, and the ethereal solution was washed with water, dried over sodium sulfate and evaporated giving 22.2 g of a colourless oil. $[\alpha]^{22} = 16.7°$ (c = 4.9, ethanol).

To the above oil, dissolved in 2-propanol (50 g) was added S-(+)-mandelic acid (9.6 g, 0.06 mole) in 2-propanol (50 g). Dry diethyl ether (50 g) was added, and the solution was left for several hours. The resulting heavy, white crystals were filtered off and washed with a mixture of 2-propanol and diethyl ether (1:1 v/v) and then dried, yielding 25 g of the title compound which melted at 148°C. $[\alpha]^{22} = 38.3°$ (c = 5.1, methanol).

The 1-H N.M.R. spectrum was in accordance with the above structure.

Chiral purity as assessed by H.P.L.C. was >99%.

Elementary Anal.	Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
	Found	C: 72.9	H: 8.1	N: 3.0	O: 16.5

j2) (-)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium (-) mandelate

The title compound was obtained from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine in an analogous manner to that described in j1) above.

Elementary Anal.	Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
	Found	C: 73.2	H: 8.1	N: 3.0	O: 16.5

The free base had an optical rotation of $[\alpha]^{22} = -15.5°$ (c = 5.0, ethanol).

The 1-(-)-mandelic acid salt had a m.p. of 147-148°C and an optical rotation $[\alpha]^{22} = -37.9°$ (c = 4.7, methanol).

The optical purity as assessed by H.P.L.C. was >99 %.

Pharmacology

Pharmacological tests performed with one compound of the invention and three prior art compounds disclosed in the above mentioned WO 89/06644 will now be described. The following compounds were used:

(A) (+)N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, hydrochloride (WO 89/06644);
(B) N,N-diisopropyl-3-bis-(2-hydroxyphenyl)propylamine hydrochloride (WO 89/06644);
(C) (+)N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenylpropylamine, hydrochloride (WO 89/06644);
(D) N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine (-) mandelic acid salt (Example 1 above).

Raised index numerals in the text below refer to literature references listed at the end of the description.

Muscarinic Receptor Binding Studies

The tissue preparations and the general methods used have been described in detail elsewhere for the parotid gland[1], urinary bladder[2], heart[3] and cerebral cortex[3], respectively. Male guinea pigs (250-400 g body weight) were killed by a blow on the neck and exsanguinated. The brain was placed on ice for dissection of the cerebral cortex (grey matter only). Urinary bladders, hearts and parotid glands were dissected in a Krebs-Henseleit buffer (pH 7.4) containing 1 mM phenyl methyl sulfonyl fluoride (PMSF, a protease inhibitor). Dissected tissues were homogenized in an ice-cold sodium-potassium phosphate buffer (50 mM, pH 7.4) containing 1 mM PMSF, using a Polytron PT-10 instrument (bladder, heart, parotid) and a Potter-Elvehjem Teflon homogenizer (cortex). All homogenates were finally diluted with the ice-cold phosphate/PMSF buffer to a final protein concentration of ≤ 0.3 mg/ml and immediately used in the receptor binding assays. Protein was determined by the method of Lowry et al. (1951)[4], using bovine serum albumin as the standard.

The muscarinic receptor affinities of the unlabelled compounds A to D identified above were derived from competition experiments in which the ability to inhibit the receptor specific binding of (-)^{3}H-QNB (1-quinuclidinyl[phenyl-4-3H] benzilate, 32.9 Ci/mmole) was monitored as previously described[3,5]. Each sample contained 10 µl of (-)^{3}H-QNB (final concentration 2 nM), 10 µl solution of test compound and 1.0 ml tissue homogenate. Triplicate samples were incubated under conditions of equilibrium, i.e., at 25°C for 60 minutes (urinary bladder), 80 minutes (heart and cerebral cortex)

or 210 minutes (parotid gland), respectively. Non-specific binding was determined in the presence of 10 µM unlabelled atropine. Incubations were terminated by centrifugation[2], and the radioactivity in the pellets was determined by liquid scintillation spectrometry[2].

IC_{50}-values (concentration of unlabelled compound producing 50% inhibition of the receptor specific (-)^{3}H-QNB binding) were graphically determined from the experimental concentration-inhibition curves. Affinities, expressed as the dissociation constants K_i, were calculated by correcting the IC_{50} for the radioligand-induced parallel shift and differences in receptor concentration, using the method of Jacobs et al. (1975)[6]. The binding parameters for (-)^{3}H-QNB (K_D and receptor densities) used in these calculations were determined in separate series of experiments[1-3]. The K_i values obtained for bladder, heart, parotid and cortex, respectively, are presented in Table 1 below.

Functional in vitro studies

Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilize for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilization period.

Carbachol (carbamylcholine chloride) was used as the standard agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by three consecutive additions of a submaximal concentration (3×10^{-6} M) of carbachol. A complete concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}-values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1)[7], where [A] is the concentration of test compound.

$$K_B = [A]/r-1 \qquad (1)$$

The K_B values obtained for compounds A, B and D identified above are shown in Table 1 below.

Table 1

Test compound	K_B nm bladder	K_i nM bladder	K_i nM heart	K_i nM parotid	K_i nM cortex
(A)	3.0	2.7	1.6	4.8	0.8
(B)		10.2	6.7	2.6	1.5
(C)	2.6	2.5	0.9	2.7	0.4
(D)	4.1	4.5	0.9	4.7	0.7

Functional in vivo studies

a) Animal preparation

Adult cats were anaesthetized with mebumal (42 mg/kg) intraperitoneally. When the animal was asleep, an infusion cannula was inserted into the foreleg vein and the cat was given alpha-chloralose. During the experiment the animal was placed on an operation table warmed up with a feedback controlled electric pad. The cat was tracheotomized. For blood pressure registration, a polyethylene catheter was inserted into the femoral artery, with the tip in aorta, and connected via a three-way stopcock to a blood pressure transducer and a Grass polygraph. Heart rate was registered by connecting a tachograph to a driver amplifier which received the signal from the blood pressure transducer. Blood flow in the central mesenteric artery was measured by an ultrasound flow probe around the artery connected to a transonic blood flow meter and then to a Grass polygraph for registration of the flow. For infusion of the test substances, compounds D and A (as identified above), a polyethylene catheter was inserted into the femoral vein three-way stopcock to a syringe placed in an infusion pump (Sage instrument).

Through an incision in the proximal urethra, a catheter was inserted into the urinary bladder. At the beginning of each experiment, this catheter was connected to an open vessel, which was filled with 38°C tempered physiological saline and placed above the animal. During this stabilization period the bladder relaxed, leading to a filling of the bladder with saline, under constant hydrostatic pressure. After the stabilization period, the bladder catheter was connected to a pressure transducer, for registration of intravesical pressure. Blood pressure, heart rate, blood flow and bladder pressure were recorded simultaneously and continuously throughout the experiment. The animals were left for at least 45 minutes to achieve steady state in cardiovascular variables before starting the experiment.

Bladder pressure was measured at 8 minutes after the end of infusion of the test substance. The surgical preparation was tested by intravenous injection of 0.25 µg/kg b.w. of noradrenalin and 0.5 µg/kg b.w. of acetylcholine.

b) Dosing

To study the dose-response relationship of compound D identified above, the substance was administered at the doses 0.000 (physiological saline), 0.003, 0.010, 0.030 and 0.100 mg/kg, respectively, with infusion during 2 minutes and an infusion volume of 1 mL/kg. Every cat got all doses and was left to reestablish at least 45 minutes between the 0.003 and 0.010 mg/kg doses, and 60 minutes between the 0.030 and 0.100 mg/kg doses.

c) Statistical methods and calculation

The results are presented in absolute values and calculated as mean value ± standard deviation

d) Results

(i) Blood pressure

In general, intravenous administration of compound D had little or no effect on the blood pressure except at dose of 0,3 mg/kg. This dose caused an increase with 10% and with 6 % for diastolic blood pressure and systolic blood pressure, respectively.

(ii) Blood flow

Intravenous administration of compound D caused an increase with 8, 17 and 21 % of the blood flow in superior mesenterica artery at 0.003, 0.01, and 0.03 mg/kg, respectively. Again at the highest dose (0.3 mg/kg) a 10% increase in blood flow was observed.

(iii) Heart rate

Intravenous administration of compound D caused a decrease with 9 % at the highest dose (0.3 mg/kg).

(iv) Bladder pressure

As appears from Fig. 1, compound D of the present invention produced a dose-dependent inhibition of the acetylcholine-induced effect on the bladder which was about ten times more efficient than that of prior art compound A.

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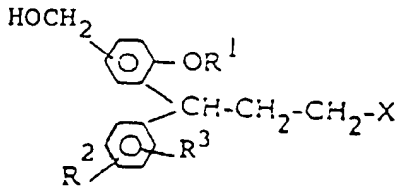
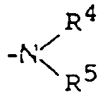
Claims

1. 3,3-Diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2 and R^3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



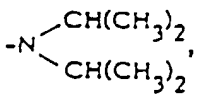
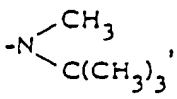
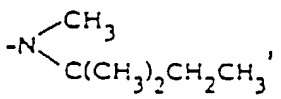
II

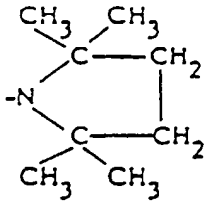
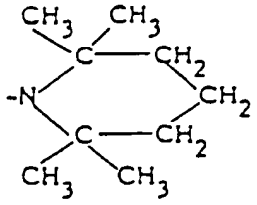
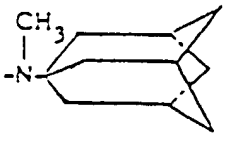
wherein each of R^4 and R^5 independently signify non-aromatic hydrocarbyl groups, which may carry one or more hydroxy groups and which together contain at least three carbon atoms, and wherein R^4 and R^5 may be joined to form a ring having no other heteroatom than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

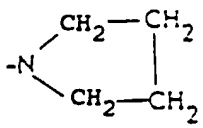
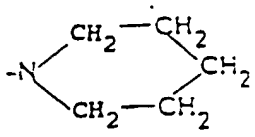
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^4 and R^5 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably at least four carbon atoms.

3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^4 and R^5 comprises a branched carbon chain.

4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

a)  , b)  , c)  ,

d)  , e)  , f) 

g)  , h) 

5. 3,3-Diphenylpropylamines according to any one of claims 1 to 4, wherein the $HOCH_2$-group is in 5-position, R^2 is hydrogen and R^3 is hydrogen or hydroxy, preferably in 2-position.

6. 3,3-Diphenylpropylamines according to claim 1, selected from N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine, its salts with physiologically acceptable acids, racemates and individual enantiomers thereof.

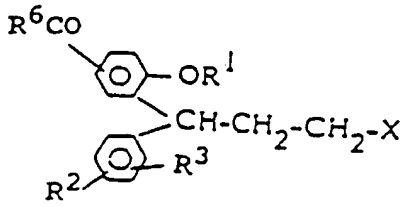
7. 3,3-Diphenylpropylamines according to any one of claims 1 to 6 for use as pharmaceutically active substances, especially as anticholinergic agents.

8. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1 to 6 and preferably a compatible pharmaceutical carrier.

9. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 6 for preparing an anticholinergic drug.

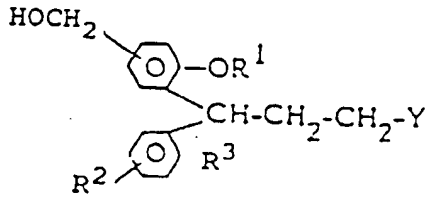
10. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1 to 6, comprising:

a) reducing the group R^6CO of a 3,3-diphenylpropylamine of formula III



III

wherein R^1 to R^3 and X are as defined above, R^6 is hydrogen or R^7O, where R^7 is hydrogen, alkyl, alkenyl, alkynyl or aryl, and any hydroxy groups may be protected, such as by methylation or benzylation, or
b) reacting a reactively esterified 3,3-diphenylpropanol of formula IV

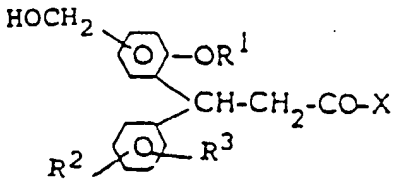


IV

wherein R^1 to R^3 are as defined above, any hydroxy groups may be protected, and wherein Y is a leaving group, with an amine of formula V

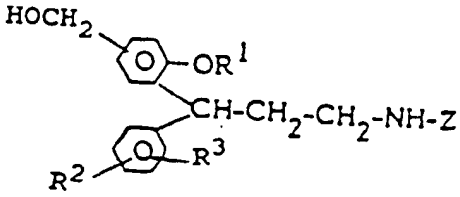
$$H\text{-}X \qquad V$$

wherein X is as defined above, or
c) reducing a 3,3-diphenylpropionamide of formula VI



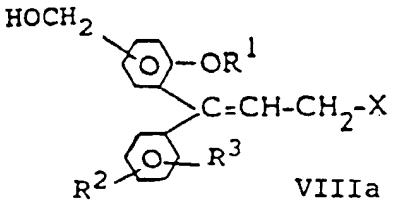
VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, or
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII

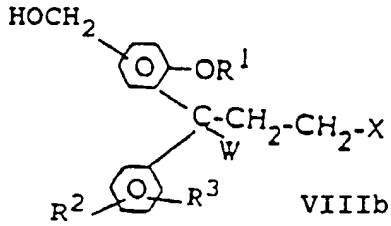


VII

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^4 and R^5 with the exception of methyl, or
e) reducing a 3,3-diphenylpropenamine of formula VIIIa or a 3,3-diphenylpropylamine of formula VIIIb

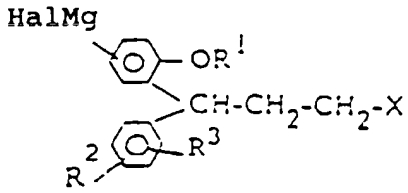


VIIIa



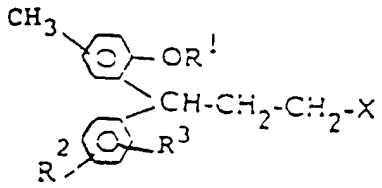
VIIIb

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, or
f) reacting a diphenylpropylamine of formula IX



IX

wherein R^1 to R^3 and X are as defined above, and Hal is halogen, with formaldehyde or a formaldehyde equivalent, or
g) oxidizing the methyl group of a diphenylpropylamine of formula X



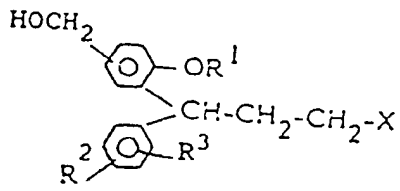
X

wherein R^1 to R^3 and X are as defined above, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono- or di-halogenation of one or both of the phenyl rings, and/or
ii) if desired converting the obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^3 is hydroxy.

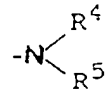
Patentansprüche

1. 3,3-Diphenylpropylamine der Formel I



I

worin R^1 für Wasserstoff oder Methyl steht, R^2 und R^3 unabhängig voneinander für Wasserstoff, Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen stehen und X für eine tertiäre Aminogruppe der Formel II



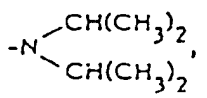
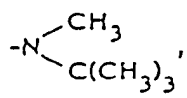
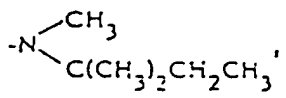
II

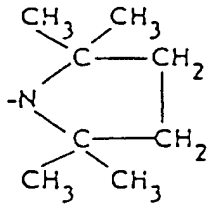
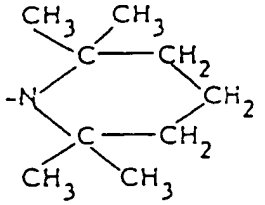
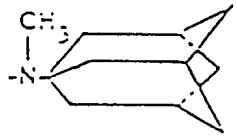
steht, in der jedes R^4 und R^5 unabhängig voneinander für nichtaromatische Kohlenwasserstoffgruppen steht, die eine oder mehrere Hydroxygruppen tragen können und die zusammen wenigstens drei Kohlenstoffatome enthalten und in der R^4 und R^5 miteinander verbunden sein können, um einen Ring zu bilden, der kein anderes Heteroatom besitzt als den Aminstickstoff, ihre Salze mit physiologisch annehmbaren Säuren und, wenn die Verbindungen in Form optischer Isomerer vorliegen können, die racemischen Gemische und die individuellen Enantiomere.

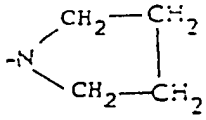
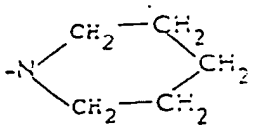
2. 3,3-Diphenylpropylamine nach Anspruch 1, dadurch **gekennzeichnet**, daß jedes R^4 und R^5 unabhängig voneinander eine gesättigte Kohlenwasserstoffgruppe, insbesondere eine gesättigte aliphatische Kohlenwasserstoffgruppe, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl bedeutet und R^4 und R^5 zusammen wenigstens drei, vorzugsweise wenigstens vier Kohlenstoffatome umfassen.

3. 3,3-Diphenylpropylamine nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß wenigstens ein Rest aus der Gruppe R^4 und R^5 eine verzweigte Kohlenstoffkette umfaßt.

4. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 3, dadurch **gekennzeichnet**, daß X für eine der folgenden Gruppen a) bis h) steht:

a)  , b)  , c)  ,

d)  , e)  , f) 

g)  , h) 

5. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 4, dadurch **gekennzeichnet**, daß die $HOCH_2$-Gruppe in der 5-Position ist, R^2 Wasserstoff und R^3 Wasserstoff oder Hydroxy, vorzugsweise in der 2-Position, ist.

6. 3,3-Diphenylpropylamine nach Anspruch 1, ausgewählt aus N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin, seinen Salzen mit physiologisch annehmbaren Säuren, Racemate und individuellen Enantiomere davon.

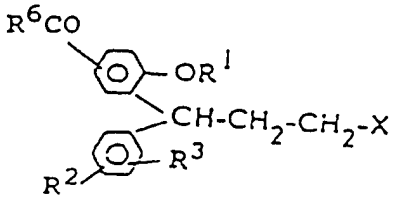
7. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 6 zur Verwendung als pharmazeutisch aktive Substanzen, insbesondere als anticholinerge Mittel.

8. Pharmazeutisches Mittel, umfassend ein 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 6 und vorzugsweise einen kompatiblen pharmazeutischen Träger.

9. Verwendung eines 3,3-Diphenylpropylamins nach einem der Ansprüche 1 bis 6 zur Herstellung eines anticholinergen Medikaments.

10. Verfahren zur Herstellung von 3,3-Diphenylpropylaminen nach einem der Ansprüche 1 bis 6, umfassend die folgenden Stufen:

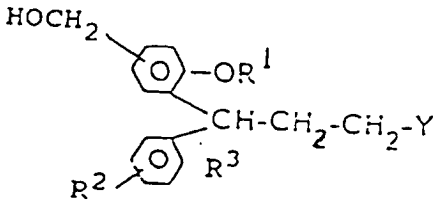
a) Reduktion der R^6CO-Gruppe eines 3,3-Diphenylpropylamins der Formel III



III

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, R^1 Wasserstoff oder R^7O ist, wobei R^1 Wasserstoff, Alkyl, Alkenyl, Alkinyl oder Aryl ist, und jegliche Hydroxygruppen z.B. durch Methylierung oder

Benzylierung geschützt sein können oder
b) Umsetzung eines reaktiv veresterten 3,3-Diphenylpropanols der Formel IV

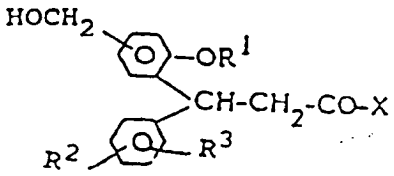


IV

in der R^1 bis R^3 die oben definierten Bedeutungen haben, jegliche Hydroxygruppen geschützt sein können und in der Y eine Austrittsgruppe ist, mit einem Amin der Formel V

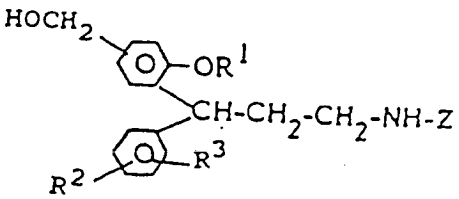
$$H - X \qquad V,$$

in der X die oben definierte Bedeutung hat oder
c) Reduktion eines 3,3-Diphenylpropionamids der Formel VI



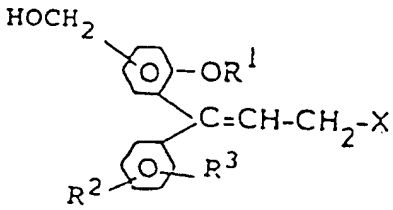
VI

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können, oder
d) N-Methylierung eines sekundären 3,3-Diphenylpropylamins der Formel VII

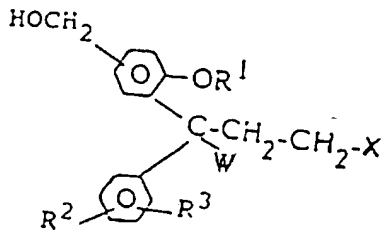


VII

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, und jegliche Hydroxygruppen geschützt sein können und in der Z die gleiche Bedeutung wie R^4 und R^5 mit Ausnahme von Methyl hat oder
e) Umsetzung eines 3,3-Diphenylpropenamins der Formel VIIIa oder eines 3,3-Diphenylpropylamins der Formel VIIIb



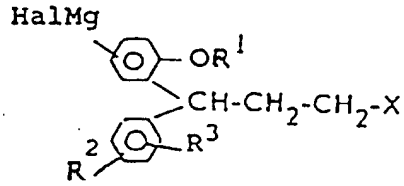
VIIIa



VIIIb

worin R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können und W für eine Hydroxygruppe oder ein Halogenatom steht oder

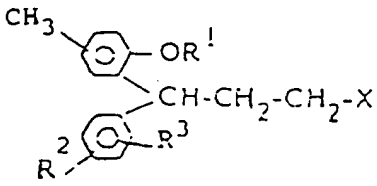
f) Umsetzung eines Diphenylpropylamins der Formel IX



IX

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und Hal für Halogen steht, mit Formaldehyd oder einem Formaldehyd-Äquivalent oder

g) Oxidation der Methylgruppe eines Diphenylpropylamins der Formel X



X

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und

i) falls nötig, Abspaltung der Hydroxyschutzgruppen in den erhaltenen Verbindungen, falls erwünscht nach Mono- oder Dihalogenierung eines oder beider Phenylringe und/oder

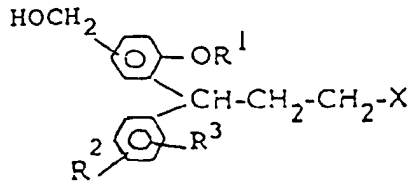
ii) falls gewünscht, Umwandlung der erhaltenen Basen der Formel I in die Salze davon mit physiologisch annehmbaren Säuren oder umgekehrt, und/oder

iii) falls gewünscht, Trennung eines erhaltenen Gemisches optischer Isomere in die individuellen Enantiomeren, und/oder

iv) falls gewünscht, Methylierung einer ortho-Hydroxygruppe in einer erhaltenen Verbindung der Formel I, in der R^1 für Wasserstoff und/oder R^3 für Hydroxy steht.

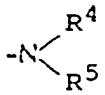
Revendications

1. 3,3-diphénylpropylamines de formule I



I

dans laquelle R^1 représente l'hydrogène ou un groupe méthyle, R^2 et R^3 représentent indépendamment l'hydrogène, un groupe méthyle, méthoxy, hydroxy, carbamoyle, sulfamoyle ou halogéno, et X représente un groupe amino tertiaire de formule II



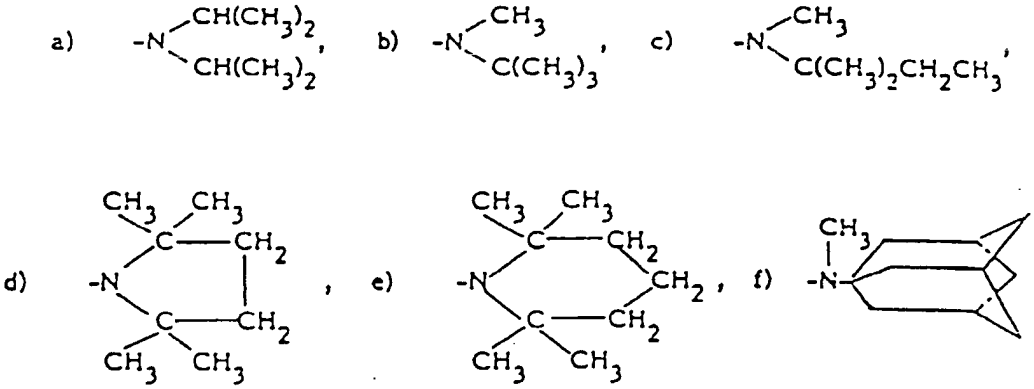
II

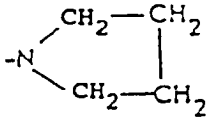
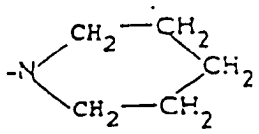
dans laquelle chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle non aromatique, qui peut porter un ou plusieurs groupes hydroxy, les groupes R^4 et R^5, conjointement, contenant au moins trois atomes de carbone, et dans laquelle R^4 et R^5 peuvent être joints en formant un noyau n'ayant aucun autre hétéroatome que l'atome d'azote d'amine, leurs sels formés avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères distincts.

2. 3,3-diphénylpropylamines suivant la revendication 1, dans lesquelles chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle saturé, notamment un groupe hydrocarbyle aliphatique saturé tel qu'un groupe alkyle en C_1 à C_8, notamment alkyle en C_1 à C_6 ou un groupe adamantyle, les groupes R^4 et R^5, conjointement, comprenant au moins trois, de préférence au moins quatre atomes de carbone.

3. 3,3-diphénylpropylamines suivant la revendication 1 ou 2, dans lesquelles au moins un des groupes R^4 et R^5 comprend une chaîne carbonée ramifiée.

4. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 3, dans lesquelles X représente l'un quelconque des groupes a) à h) suivants :



g)  , h) 

5. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 4, dans lesquelles le groupe $HOCH_2$ est en position 5, R^2 représente l'hydrogène et R^3 représente l'hydrogène ou un groupe hydroxy, de préférence en position 2.

6. 3,3-diphénylpropylamines suivant la revendication 1, choisies entre la N,N-diisopropyl-3-(2-hydroxy-5-hydroxyméthylphényl)-3-phénylpropylamine, ses sels formés avec des acides physiologiquement acceptables, ses racémates et les énantiomères distincts correspondants.

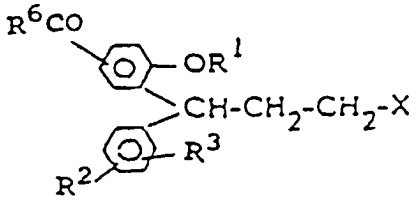
7. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, destinées à être utilisées comme substances pharmaceutiquement actives, notamment comme agents anticholinergiques.

8. Composition pharmaceutique comprenant une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 et, de préférence, un support pharmaceutiquement compatible.

9. Utilisation d'une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 pour la préparation d'un médicament anticholinergique.

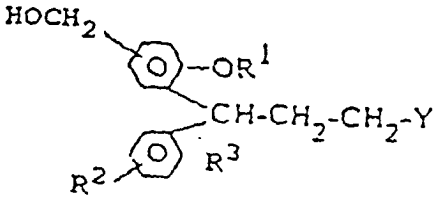
10. Procédé pour la préparation de 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, comprenant :

a) la réduction du groupe R^6CO d'une 3,3-diphénylpropylamine de formule III



III

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, R^6 représente l'hydrogène ou un groupe R^7O, dans lequel R^7 représente l'hydrogène, un groupe alkyle, alcényle, alcynyle ou aryle, et n'importe quels groupes hydroxy peuvent être protégés, par exemple par méthylation ou benzylation, ou
b) la réaction d'un 3,3-diphénylpropanol, estérifié réactivement, de formule IV

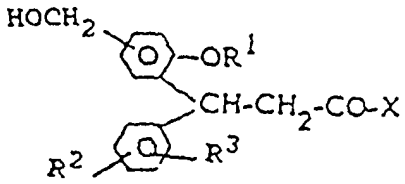


IV

dans laquelle R^1 à R^3 répondent aux définitions précitées, n'importe quels groupes hydroxy pouvant être protégés, et dans laquelle Y représente un groupe partant, avec une amine de formule V

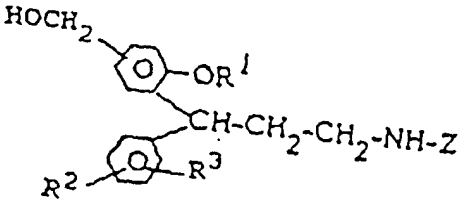
H - X V

dans laquelle X répond à la définition précitée, ou
c) la réduction d'un 3,3-diphénylpropionamide de formule VI



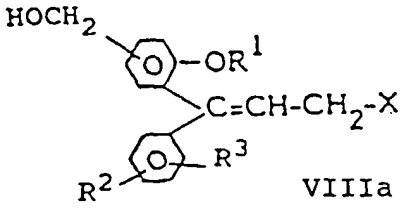
VI

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, ou
d) la N-méthylation d'une 3,3-diphénylpropylamine secondaire de formule VII

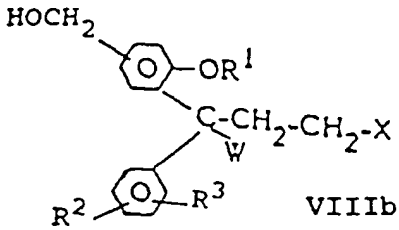


VII

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, et dans laquelle Z répond à la même définition que R^4 et R^5 à l'exception du groupe méthyle, ou
e) la réduction d'une 3,3-diphénylpropène-amine de formule VIIIa ou d'une 3,3-diphénylpropylamine de formule VIIIb

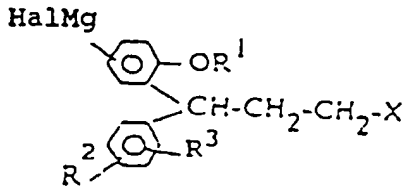


VIIIa



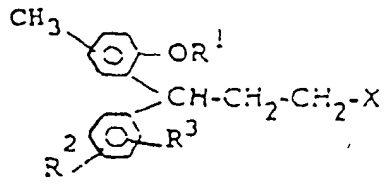
VIIIb

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, et W représente un groupe hydroxy ou un atome d'halogène, ou
f) la réaction d'une diphénylpropylamine de formule IX



IX

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, et Hal représente un halogène, avec le formaldéhyde ou un équivalent de formaldéhyde, ou
g) l'oxydation du groupe méthyle d'une diphénylpropylamine de formule X



X

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, et

i) lorsque cela est nécessaire, la scission des groupes protecteurs de la fonction hydroxy dans les composés obtenus, si besoin après mono- ou dihalogénation d'un des ou des deux noyaux phényle, et/ou
ii) si cela est désiré, la transformation des bases obtenues de formule I en leurs sels formés avec des acides physiologiquement acceptables, ou vice versa, et/ou
iii) si cela est désiré, la séparation d'un mélange obtenu d'isomères optiques en les énantiomères distincts, et/ou
iv) si cela est désiré, la méthylation d'un groupe ortho-hydroxy dans un composé obtenu de formule I, dans laquelle R^1 représente l'hydrogène et/ou R^3 représente un groupe hydroxy.

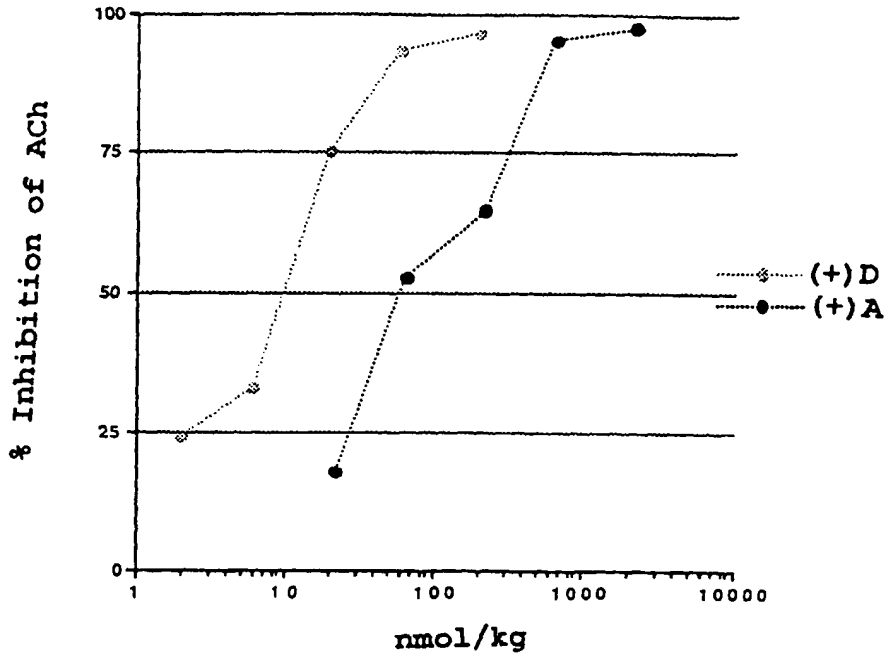


FIG. 1

ODWS 24.7.03

AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General dated the eleventh day of October, 1957, under Section 33, of the Patents Act, 1949.

PATENT SPECIFICATION

GB 685,696

Date of Application and filing Complete Specification: Oct. 13, 1949.

No. 26316/49.

Application made in United States of America on Nov. 23, 1948.

Complete Specification Published: Jan. 7, 1953.

Index at acceptance:—Class 2(iii), B4a(2:4), B4(d:e), C1a(1:10), C1b(1:2), C1e4k(3:4:6:8), C1e5k(4:6:8), C1e6k(4:6:8), C1f2a(2:3), C1f2c(4:5:6), C1f2d(1:2:3), C2a(3:5:14), C2b3 (a4:b:f), C2b3g(1:7), C2b(4:9), C(2r17:3a:12), C3a13a3(a4:b3:f3), C3a13c(1c:2c:3c:6c:9), C3a13c10(f:h), C3a14a(3d:5:8d).

COMPLETE SPECIFICATION

Process for the Manufacture of Anti-Histaminic Compounds

We, SCHERING CORPORATION, having a place of business at 2, Broad Street, Bloomfield, County of Essex, State of New Jersey, United States of America, a corporation organized under the laws of the State of New Jersey, United States of America, (Assignee of NATHAN SPERBER, residing in Bronx, County of Bronx, State of New York, United States of America, and DOMENICK PAPA, residing in Brooklyn, County of Kings, State of New York, United States of America, both Citizens of the United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to new substances of interesting and important physiological properties and a process for their manufacture. More specifically, the invention relates to the preparation of compounds having pronounced antihistaminic activity.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

In specifications Nos. 307,304 and 646,198 (both as open to public inspection under Section 91 of the Patents Acts 1907—1946) general methods are described for the conversion of ketones of the formula:

$$R^3 . CO . X . NR^1R^2$$

by Grignard reaction into carbinols:

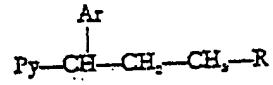
$$\begin{matrix} R_3 \\ R_4 \end{matrix} > C(OH) . X . NR^1R^2$$

and in Specification No. 646,198 for the subsequent replacement of the hydroxyl group by hydrogen, R^1, R^2, R^3 and R^4 being monovalent organic radicals (NR^1R^2 may be a nitrogen ring residue) and X being a divalent linking group. The products are stated to have good musculotropic antispasmodic activity accompanied by low neurotropic antispasmodic activity. In Specification No. 646,198 as open to public inspection under Section 91 *N*-(3-phenyl - 3-*cyclo*hexylpropyl)-piperidinehydrochloride, obtained in this manner from N-piperidylpropiophenone and *cyclo*hexyl bromide, is said to have 12 times the musculotropic antispasmodic activity of papaverine.

We have now found that certain com-

pounds obtainable by similar general reactions possess to an outstanding degree antihistaminic and antianaphylactic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in more than 90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

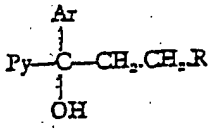
The selected compounds showing this advantage have the general formula



wherein Py stands for 2-pyridyl, Ar for phenyl or an alkyl-, alkoxy-, dialkylamino, chloro- or bromophenyl or for 2-thienyl, and R for a dialkylamino-, piperidino-, pyrrolidino-, or morpholino-group.

Throughout this specification the terms alkyl and alkoxy are used to denote groups having less than seven carbon atoms.

The compounds of the invention are produced by a process comprising the step of condensing a ketone $Ar.CO.CH_2.CH_2.R$, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol

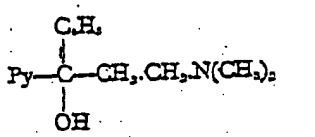


followed by replacement of the hydroxyl group by a hydrogen atom. The resulting bases may be converted into their salts by the usual methods.

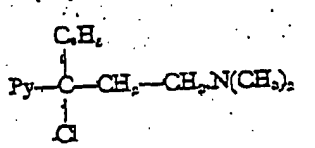
Thus from β - dimethylaminopropiophenone (I)

$$C_6H_5.CO.CH_2CH_2.N(CH_3)_2 \qquad (I)$$

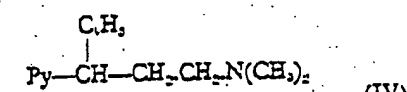
there is obtained 1-(2'-pyridyl)-1-Phenyl-3-dimethylaminopropanol-1 (II):



The carbinol (II) may be reacted with thionyl chloride to form the chloro-compound (III):



which on reduction with zinc dust and acetic acid gives in good yield the desired 1-phenyl-1-(2'-pyridyl)-3-dimethylaminopropane (IV)



(IV)

By a similar series of reactions compounds in which the phenyl group carries alkyl, alkoxyl, dialkylamino, chlorine or bromine substituents may be prepared. For the *p*-chloro-compound, for example the starting material is the ketone

p-$Cl.C_6H_4.CO.CH_2.CH_2.N(CH_3)_2$,

obtained by the Mannich reaction from *p*-chloroacetophenone, dimethylamine and formaldehyde.

By using diethylamine, piperidine, pyrrolidine or morpholine in place of dimethylamine the corresponding diethylamino-, piperidino-, pyrrolidino- or morpholino- ketone may be prepared.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2-pyridyl) - N,N - dimethypropylamine of Example I are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrogen chloride into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions comprise non-toxic salts.

EXAMPLE I.

1-Phenyl-1-(2'-pyridyl) - 3 - dimethylaminopropane.

The intermediate carbinol, phenyl - (2'-

pyridyl)-β-dimethylaminoethylcarbinol (II), is prepared as follows:

β-Dimethylaminopropiophenone hydrochloride (0.1 mole) is dissolved in 50 cc. of water and cooled in an ice-bath. The free base is liberated with ice and 10% sodium carbonate solution, and the oil is taken up in ether. The ether layer is washed with water and dried over anhydrous potassium carbonate. Upon removal of the ether, the free base is obtained.

A solution of 0.2 moles of 2-pyridyllithium in 250 ml. of ether is prepared and after cooling to −40° C., a solution of 18 g. of β-dimethylaminopropiophenone in 50 cc. of ether is added dropwise with stirring over a period of ½ hour. Upon completion of the reaction, the temperature is allowed to rise to −15° C. and the reaction mixture is stirred at this temperature for one hour. The contents of the flasks are decomposed with ice and hydrochloric acid and then made basic with gaseous ammonia. The resulting oil is taken up in ether, the ether evaporated and the residue distilled. The carbinol is a viscous, yellow syrup, boiling at 176—180° C./2 mm.

The carbinol (II) is converted to the propylamine as follows:

Phenyl-(2'-pyridyl) - β - dimethylaminoethyl carbinol (II) (0.1 mole) is dissolved in 250 cc. of dry benzene and thionyl chloride (0.15 mole) added, keeping the temperature between 0 and 10° C. The reaction is allowed to come to room temperature, stirred for an additional ½ hour, and then made basic with a dilute solution of sodium hydroxide. The benzene layer is separated, dried and concentrated *in vacuo* leaving a viscous, purple oil. The crude phenyl-(2'-pyridyl)-β-dimethylaminoethyl-methylchloride is dissolved in 200 cc. of glacial acetic acid and zinc dust (0.3 mole) added. The reaction mixture is stirred and heated on the steam bath for 6 hours, the zinc salts filtered and the filtrate concentrated *in vacuo*. The thick syrup is made alkaline with dilute sodium hydroxide and the oil which separates is extracted with ether. The ether layer is dried, concentrated and the residue distilled.

EXAMPLE II.

1(*p*-Methoxyphenyl)-1-(2' - pyridyl) - 3-dimethylaminopropane.

This compound is prepared by the procedure described in Example I using *p*-methoxyacetophenone in a Mannich condensation with formaldehyde and dimethylamine hydrochloride to prepare β-dimethylamino-*p*-methoxypropiophenone. The latter is then carried through the series of reactions described in Example I. The substituted propylamine is a pale yellow, viscous liquid; b.p. 172—175° C./1.5 mm.

EXAMPLE III.

1(*p*-Chlorophenyl)-1-(2'-pyridyl)-3-dimethylaminopropane.

Using *p*-chlorophenylacetophenone in the Mannich reaction followed by the 2-pyridyllithium reaction and the series of reactions described in Example I the corresponding propylamine is prepared; b.p. 139—141° C./1.0 mm.

EXAMPLE IV.

1-(Phenyl)-1-(2'-pyridyl)-3-diethylaminopropane.

By substituting β-diethylaminopropiophenone hydrochloride for the dimethylamino compound in Example I there is obtained the compound of this example; b.p. 156—157° C./2.0 mm.

EXAMPLE V.

1-(Phenyl)-1 - (2'-pyridyl)-3-N - piperidinopropane.

By substituting piperidine hydrochloride for dimethylamine hydrochloride in Example I, the piperidino compound is obtained as a viscous yellow liquid boiling at 176—177° C/3.5 mm.

EXAMPLE VI.

1-Phenyl-1-(2'-pyridyl)-3-(N-pyrrolidyl)-propane.

The β-(1-pyrrolidyl)propiophenone is obtained by the Mannich condensation of acetophenone with formaldehyde and pyrrolidine. The free base is liberated from the hydrochloride and then is reacted with 2-pyridyllithium, followed by further reactions in accordance with the procedure of Example I. The pyrrolidylpropane is obtained as a pale yellow oil boiling at 164—166° C./2—3 mm.

EXAMPLE VII.

1-(*p*-Chlorophenyl)-1-(2'-pyridyl)-3-(N-pyrrolidyl)propane.

This compound is obtained exactly as described for the unsubstituted compound of the above example using *p*-chloroacetophenone in place of acetophenone. The halogenated compound of this example is a yellowish liquid boiling at 175—177° C./1—2 mm.

The following are other typical amines prepared by the methods of the invention:

1-(2'-Thienyl)-1-(2''-pyridyl)-3 - dimethylaminopropane, b.p. 154° C./2 mm.

1-(*p*-Methylphenyl)-1-(2'-pyridyl) - 3 - dimethylaminopropane, b.p. 137—140° C./0.5 mm.

1-(4' - Dimethylaminophenyl) - 1 - (2''-pyridyl)-3-dimethylaminopropane, b.p. 183—185° C./1.5 mm.

1-(2',3'-Dimethoxyphenyl)-1 - (2''-pyridyl)-3-dimethylaminopropane, b.p. 195—200° C./1—2 mm.

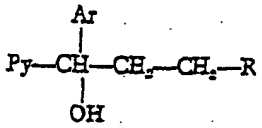
1-(*p*-Isopropylphenyl)-1-(2' - pyridyl) - 3-dimethylaminopropane, b.p. 147—152° C/1.0 mm.

What we claim is:—

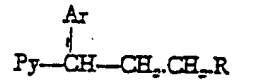
1. The step in the production of pyridyl aliphatic amines and their salts which consists in reacting a ketone of formula

$$Ar.CO.CH_2.CH_2R$$

wherein Ar stands for phenyl or for an alkyl-, alkoxy-, dialkylamino-, chloro- or bromophenyl and R stands for a dialkylamino-, piperidino-, pyrrolidino- or morpholino-group, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol

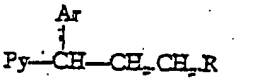


wherein Py stands for 2-pyridyl followed by replacement of the hydroxyl group in the resulting carbinol by hydrogen to give the compound.



and conversion of the product, if desired, into its salts.

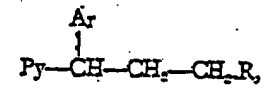
2. The step in the production of pyridyl-aliphatic amines and their salts as claimed in Claim 1 comprising the conversion of the carbinol into the corresponding halide, e.g. by the action of thionyl chloride and replacement of the halogen by hydrogen, e.g. by reduction with zinc dust and acetic acid, to give a compound of formula



and conversion of this product if desired, into its salts.

3. The steps as claimed in either of the preceding claims in which Ar stands for phenyl or p-chlorophenyl and R for dimethylamino or N-pyrrolidyl.

4. Process for the production of saturated compounds of the formula



substantially as described with reference to each of the foregoing Examples.

5. 3-(2¹-Pyridyl)-3-arylpropylamines, whenever produced by the process claimed in any of the preceding claims.

6. Salts of 3-(2¹-pyridyl)-3-aryl-propylamines whenever produced by the process claimed in any of Claims 1—3.

Dated this 13th day of October, 1949.

URQUHART-DYKES & LORD,
Maxwell House, 11, Arundel Street, Strand,
London, W.C.2, and
12, South Parade, Leeds 1,
Chartered Patent Agents.

Reference has been directed in pursuance of Section 9, sub-section (1) of the Patents Act, 1949 to Patent No. 689,234.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1957.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

689,835

Date of Application and filing Complete Specification: Oct. 23, 1950.

No. 27281/49.

Application made in Germany on Sept. 5, 1949.

Complete Specification Published: April 8, 1953.

Index at acceptance:—Class 2(iii), B4a(2: 4), B4e, C2a(3: 5), C2r17.

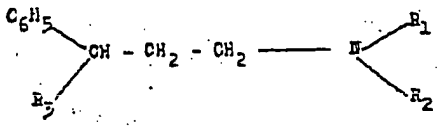
COMPLETE SPECIFICATION

Manufacture of Para-Aminosalicylates

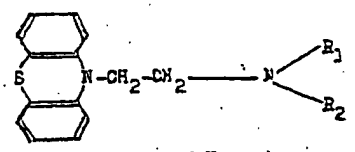
We, MICHAEL ERLENBACH and ADOLF SIEGLITZ, both German citizens, of Georg Voigtsstrasse 12, Frankfurt, Main, Germany, and Orienstrasse, Bad Soden, Taunus, Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The usual anti-histaminic substances are generally applied for therapeutic purposes in the form of salts of the corresponding bases with inorganic acids, the potency of the salt corresponding to that of the base diminished in proportion to the weight of the acid combined with the base. (Compare "Die Pharmazie," 1947, page 495; "Chemisches Zentralblatt," Verlag Chemie, 1947, Vol. I, pages 446 *et seq.*).

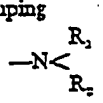
The present invention is based on the observation that the salts of anti-histaminic bases of the general formula



or



in which R_1 and R_2 each represents a methyl group or the grouping



represents a pyrrolidino group, and R_2 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid are distinguished by a surprisingly high anti-histaminic action. This action considerably exceeds that of the anti-histaminic base and the known salts thereof.

Although para-aminosalicylic acid itself exhibits a certain anti-histaminic effect, this does not suffice to explain the enhanced action of the salts, which is due to a synergistic action.

The salts of anti-histaminic bases with para-aminosalicylic acid are made in accordance with this invention by reacting equimolecular proportions of para- aminosalicylic acid with an anti-histaminic base, or by the double decomposition of an alkali salt or alkaline earth metal salt of para-aminosalicylic acid with a salt of an anti-histaminic base with an inorganic acid.

As examples of salts of anti-histaminic bases in accordance with the invention there may be mentioned especially 1-phenyl-1-pyridyl - (2^1) - 3-dimethylaminopropane para-aminosalicylate, 1-phenyl-1-pyridyl-(2^1)-3-N-pyrrolidinopropane para - aminosalicylate, 1-phenyl - 1 - thiazolyl - (2^1) - 3-N-pyrrolidino-propane para-aminosalicylate and 10-dimethyl-aminoethyl-phenthiazine para-aminosalicylate.

The following examples illustrate the invention, the parts being by weight unless otherwise stated, and the relationship of parts by weight to parts by volume being the same as that of the kilogram to the litre:

EXAMPLE 1.

1-PHENYL-1-PYRIDYL-(2^1)-3-DIMETHYLAMINO-PROPANE PARA-AMINOSALICYLATE.

Equivalent quantities of 1-phenyl-1-pyridyl-(2^1) - 3'- dimethyl - aminopropane and para-aminosalicylic acid are separately dissolved in ethyl acetate, and the two solutions are mixed together. The salt named above very soon separates in a practically quantitative yield. It melts at temperatures of 144—145° C. with decomposition, and is twice as potent as the corresponding phosphate.

EXAMPLE 2.

1-PHENYL-1-PYRIDYL-(2^1)-3-N-PYRROLIDINO-PROPANE PARA-AMINOSALICYLATE.

5.52 parts of 1-phenyl-1-pyridyl-(2^1)-3-N-

[*Price* 2/8]

pyrrolidino-propane are dissolved in 40 parts by volume of acetone, and 6.12 parts of para-aminosalicylic acid are dissolved in 30 parts by volume of acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates which melt at 171—172° C. with decomposition. The yield is nearly quantitative. The para-amino-salicylate is soluble in water and about twice as potent as the corresponding phosphate.

EXAMPLE 3.

1-PHENYL-1-THIAZOLYL-(2')-3-N-PYRROLIDINOPROPANE PARA-AMINOSALICYLATE.

Equivalent quantities of para-aminosalicylic acid and 1-phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropane are separately dissolved in acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates melting at 161—162° C. with decomposition. The yield is practically quantitative. The product is soluble in water and twice as potent as the corresponding phosphate.

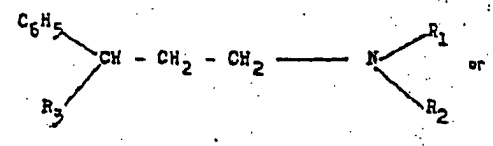
EXAMPLE 4.

10-DIMETHYLAMINOETHYL-PHENTHIAZINE PARA-AMINOSALICYLATE.

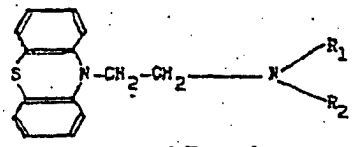
10 parts of 10-dimethylaminoethyl-phenthiazine hydrochloride are dissolved, while gently heating, in 120 parts of water, and the solution so obtained is mixed with a solution of 7 parts of sodium para-amino-salicylate in 50 parts by volume of water. The oily solution, which separates, rapidly becomes solid on rubbing. 13.3 parts of the para-aminosalicylate are obtained as a colourless salt which is sparingly soluble in water and readily soluble in hot acetone, in hot methyl alcohol and in ethyl acetate. It decomposes at 159—160° C. and is twice as potent as the hydrochloride of 10-dimethyl-aminoethyl-phenthiazine.

What we claim is:—

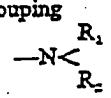
1. A salt of an anti-histaminic base of the general formula



or



in which R_1 and R_2 each represent a methyl group or the grouping



represents a pyrrolidino group, and R_3 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid.

2. 1-Phenyl-1-pyridyl-(2')-3-dimethylamino-propane para-aminosalicylate.

3. 1-Phenyl-1-pyridyl-(2')-3-N-pyrrolidino-propane para-aminosalicylate.

4. 1-Phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropane para-aminosalicylate.

5. 10-Dimethylaminoethyl-phenthiazine para-aminosalicylate.

6. A process for the manufacture of a salt of an anti-histaminic base claimed in any one of claims 1—5, wherein para-aminosalicylic acid and the anti-histaminic base are reacted together in equimolecular proportions or an alkali salt or an alkaline earth metal salt of para-aminosalicylic acid is reacted with a salt of the anti-histaminic base with an inorganic acid.

7. A process for the manufacture of a salt of an anti-histaminic base conducted substantially as described in any one of Examples 1—4 herein.

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Quality House, Quality Court, Chancery Lane, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

GB 690,274

Date of Application and filing Complete Specification: Oct. 18, 1948.

No. 27020/48.

Application made in United States of America on Oct. 28, 1947.

Complete Specification Published: April 15, 1953.

Index at acceptance:—Classes 2(iii), B4a(1: 2), B4(c: d), C1a10, C1b(1: 2), C2a[illegible], C2b3(a4: b: d: f), C2b3g(1: 8), C2b(18: 20), C2r[illegible]; and 81(i), B11b1(a: c: g: i), B11b2(a: c: g: i).

COMPLETE SPECIFICATION

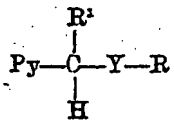
Antihistaminic Substances

We, SCHERING CORPORATION, a corporation of the State of New Jersey, of 2, Broad Street, Bloomfield, New Jersey, United States of America, (Assignees of NATHAN SPERBER, 1456, Minford Place, Bronx, New York, DOMENICK PAPA, 17th Avenue, Brooklyn, New York and ERWIN SCHWENK, 10, Crestmont Road, Montclair, New Jersey, United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed to be particularly described and ascertained in and by the following statement:—

The invention relates to the manufacture of new substances of interesting and important physiological properties and more particularly to the manufacture of pyridyl substituted alkanes which have been found to be highly effective against histamine-induced allergic reactions.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance, they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

It has been generally considered that only those substances which are derivatives of ethanolamine and ethylenediamine show pronounced anti-histaminic and antianaphylactic activity. It has now been found that pyridyl aliphatic amines of the general formula

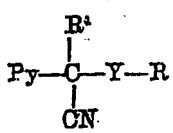


wherein Y stands for an alkylene group having 2 or 3 carbon atoms, Py is a pyridine ring which may be substituted by a halogen, alkoxy or lower alkyl group, R represents a dialkylamino, piperidino, morpholino, or iminazolinyl-group, and R^1 represents an alkyl, aryl, aralkyl *cyclo*alkyl or heterocyclic group or an alkyl, alkoxy, dialkylamino, chloro or bromo derivative of such groups, and the salts thereof with inorganic and organic acids, possess to an extremely high degree antihistaminic and antianaphylactic activity.

Throughout this Specification and claims it is to be understood that by the terms "alkyl," "alkoxy" (or "alkoxyl") and "dialkylamino" we mean groups in which the alkyl is a lower alkyl, i.e. contains not more than four carbon atoms.

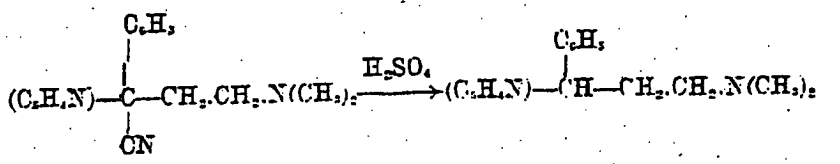
Clinical studies with representative members of the compounds of this invention have demonstrated extremely favorable antihistaminic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in 85—90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

The method of the invention comprises the hydrolysis and decarboxylation of the nitriles of the general formula



in which Py, Y, R and R' have the significance above mentioned.

When the nitriles are treated with a strong acid, the nitriles are hydrolysed and decarboxylated to the compounds of the invention as illustrated by the following equation:



Suitable nitriles for use in making the compounds of the invention may be made (as described in co-pending Application No. 25947/48 (Serial No. 666,778) by:

(a) condensing a pyridyl or alkylpyridyl halide with an alkane or substituted alkane nitrile to form a pyridyl alkane nitrile and thereafter condensing the latter product with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide;

(b) condensing an alkane, or substituted alkane, nitrile with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide and condensing the product with a pyridyl or alkylpyridyl halide; or

(c) condensing in one operation an alkane, or substituted alkane nitrile and a pyridyl or alkylpyridyl halide with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide.

The condensations are advantageously effected by heating the reactants in an organic solvent, such as toluene or xylene or in liquid ammonia, in the presence of condensation catalysts, such as alkali metals, alkali metal amides, alkali metal alkoxides, or alkali metal organo compounds, for example, butyllithium or triphenylmethyl sodium.

The following specific example is illustrative of the method and products of the invention.

EXAMPLE.

3-PHENYL-3-(2'-PYRIDYL)-N,N-DIMETHYLPROPYLAMINE.

To 400 g. of α-phenyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile there is added 2,000 g. of 80% sulfuric acid. The mixture is heated with stirring at 140—150° C. for 24 hours. After dilution with ice and water, the aqueous sulfuric acid solution is made alkaline with ammonia gas. The oil which separates out is extracted with ether. The extract is dried, and, after removing the ether, the residue is distilled giving the 3-phenyl-3-(2'-pyridyl) - N,N - dimethylpropylamine, b.p. 139—142° C./1—2 mm.

In addition to the hydrolysis and decarboxylation of the nitriles with 80% sulfuric acid, the conversion may be effected in other ways. For example:

(a) One part of the nitrile and ten parts of 48% hydrobromic acid are refluxed for a period of 50—60 hours. The aqueous hydrobromic acid is removed *in vacuo*. The residue is made alkaline with gaseous ammonia and the oil which separates is extracted with ether. The ether residue is treated with a saturated alcoholic solution of picric acid heated to boiling and filtered. The insoluble picrate is washed with boiling alcohol. This purification process removes any starting material which, unlike the amine, forms an alcohol soluble picrate. The insoluble picrate is then decomposed with dilute sodium hydroxide, the amine is isolated by extraction with ether and purified by distillation.

(b) To one part of the nitrile there is added five parts of 80% sulfuric acid and one part of 48% hydrobromic acid. The mixture is heated at a temperature of 130—140° C. for about 30—40 hours and the reaction mixture worked up as in method (a).

(c) One part of the nitrile is refluxed with concentrated hydrochloric acid for about 60 hours. The amine thus formed is isolated and purified as described under method (a).

The following compounds having substantial antihistaminic activity may be made from the corresponding nitriles by the methods of the Example:

3-Phenyl-3-(2'-pyridyl)-N,N - diethylpropylamine, a yellow oil boiling at 156° C./1 mm., from α-phenyl-α-(β-diethylaminoethyl)-2-pyridylacetonitrile.

4-Phenyl-3-(2'-pyridyl)-N,N-dimethylbutylamine, boiling at about 135° C./0.5 mm., from α-benzyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(2'' - Thienyl)-3-(2' - pyridyl) - N,N-dimethylpropylamine, a pale yellow oil boiling at 154° C./2 mm., from α-(2''-thienyl)-α-(β' - dimethylaminoethyl) - 2-pyridylacetonitrile.

4-(2¹¹-Thienyl)-3-(2¹-pyridyl)-N,N-dimethylbutylamine, boiling at 130—133° C./0.1 mm., from α-(2¹-thienylmethyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Methylphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 130—135° C./0.5 mm., from α-(*p*-methylphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Methoxyphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 137—142° C./0.5 mm., from α-(*p*-Methoxyphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Isopropylphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at 144—147° C./1mm., from α-(*p*-isopropylphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-Phenyl-3-(6¹-methyl-2¹-pyridyl)-N,N-dimethyl-propylamine, boiling at 171—175° C./1 mm., from α-(β¹-dimethylaminoethyl)-α-(6-methyl-2-pyridyl)-phenylacetonitrile.

3-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 147—152° C./0.5 mm., from α-(*p*-bromophenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

4-Phenyl-4-(2¹-pyridyl)-2-(dimethylamino)-butane, from α-phenyl-α-(2-pyridyl)-γ-(dimethylamino)-valeronitrile.

4-Phenyl-4-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-phenyl-α-(2-pyridyl)-γ-(dimethylaminomethyl)-butyronitrile.

3-Phenyl-2-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-benzyl-α-(2-pyridyl)-β-dimethylaminopropionitrile.

3-Cyclohexyl-3-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-cyclohexyl-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-Cyclohexyl-4-(2¹-pyridyl)-N,N-dimethylbutylamine, from β-cyclohexyl-α-(β-dimethylaminoethyl)-α-(2-pyridyl)-propionitrile.

3-(5¹¹-Bromo-2¹¹-thienyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-(5-bromo-2-thienyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

4-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-(*p*-bromobenzyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2¹-pyridyl)-N,N-dimethylpropylamine of the Example are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrochloric acid into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

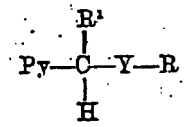
4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms, such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions preferably comprise non-toxic salts in admixture with sodium carbonate and boric acid and are sterilized before use.

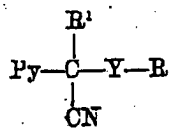
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the manufacture of antihistaminic substances of the general formula:



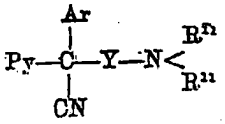
where Py represents a pyridine residue which may carry halogen, alkyl or alkoxy as substituents, Y stands for an alkylene group having 2 or 3 carbon atoms, R represents a dialkylamino-, piperidino-, morpholino- or iminazolino-group and R^1 stands for alkyl, aryl, aralkyl, cycloalkyl or a heterocyclic residue, which may carry as substituents alkyl, alkoxyl, dialkylamino, chlorine or bromine, and of salts of such compounds, said process comprising the hydrolysis and decarboxylation of a nitrile having

the formula:—



by reaction with a strong acid, e.g. with 80% sulphuric acid.

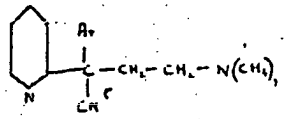
2. A process as claimed in Claim 1 in which the nitrile has the formula



where Py and Y have the same significance as in Claim 1, Ar stands for an aryl group, and either R^{11} is an alkyl group or $N<^{R^{11}}_{R^{11}}$ stands for a piperidine residue.

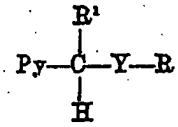
3. A process as claimed in Claim 2 in which Py is 2-pyridyl, Ar is phenyl or *p*-chlorophenyl, and R^{11} is methyl.

4. A process for the manufacture of 3-phenyl- and 3-*p*-chlorophenyl - 3 - (2'-pyridyl) - N,N - dimethylpropylamines, and of salts of these, by hydrolysis and decarboxylation of the nitriles of formula



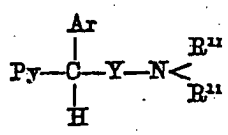
(where Ar stands for phenyl or *p*-chlorophenyl) by reaction with a strong acid, e.g. with 80% sulphuric acid, the base produced being converted into salts as desired.

5. Compounds of the formula:



where Py, R and R^1 have the same significance as in Claim 1 and salts thereof whenever produced by the process of any of the preceding claims or by an obvious chemical equivalent of such process.

6. Compounds of the formula:



in which Py and Y have the same significance as in Claim 1, Ar stands for phenyl, a chlorophenyl, an alkylphenyl or an alkoxyphenyl, and R^{11} stands for alkyl and salts thereof whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

7. Compounds as claimed in Claim 6 in which Ar is phenyl or *p*-chlorophenyl, Y is $.CH_2.CH_2.$ and R^{11} is methyl, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

8. Compounds as claimed in Claim 6 in which Py is 2-pyridyl. Y is $.CH_2.CH_2.$, and $N<^{R^{11}}_{R^{11}}$ stands for a dialkylamino group or for the N-piperidino radical, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

Dated this 18th day of October, 1948.

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Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

GB 692,931

Date of Application and filing Complete Specification: March 23, 1950.
No. 8128/49.
Application made in Germany on Nov. 9, 1948.
Application made in Germany on Dec. 2, 1948.
Application made in Germany on Dec. 24, 1948.
Complete Specification Published: June 17, 1953.

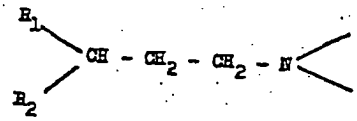
Index at acceptance:—Classes 2(iii), B4a(1: 2: 3: 4), B4(d: e), C2a(3: 14), C2b3(a4: b: g8), C2(b18: r17: s16: t16).

COMPLETE SPECIFICATION

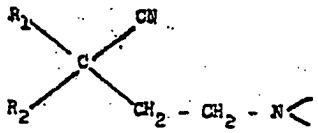
Basically Substituted Propane Compounds and the Manufacture thereof

We, MICHAEL ERLENBACH and ADOLF SIEGLITZ, both German citizens, and of Georg Voigtstrasse 12, Frankfurt (Main), Germany, and Oranienstrasse, Bad Soden (Taunus), Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention consists in a process for the manufacture of the basic compounds of the general formula



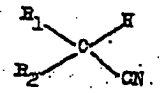
in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula



in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

As the alkali hydroxide there may be used potassium hydroxide.

The nitriles used as starting materials in the present process may be obtained by reacting a nitrile of the general formula

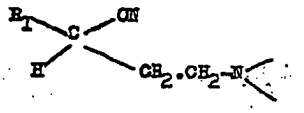


in which R_1 and R_2 have the meanings given above, with a basically substituted alkyl halide of the general formula

$$Hal—CH_2—CH_2—N<$$

in which N< has the meaning given above, in the presence of sodamide or another agent capable of eliminating hydrogen halide. Halides of this kind are, for instance, N-β-chlorethyl-dimethylamine, N-β-chlorethyl-diethylamine, 1-chloro-2-dimethylamino-propane, N-β-chlorethyl-piperidine, N-β-chlorethyl-pyrrolidine and N-β-chlorethyl-morpholine.

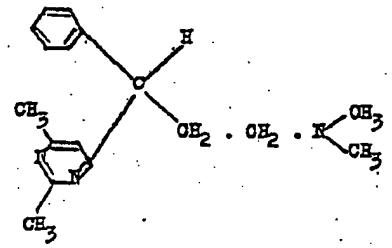
Alternatively the nitriles may be obtained by reacting a nitrile of the general formula



in which R_2 and N< have the meanings given above, with a-halogen-substituted heterocyclic compound in the presence of sodamide or another agent capable of eliminating hydrogen halide. As halogen-substituted heterocyclic compounds there may be used, for example 2-chloropyridine, 2-chlorothiazole, 2:6-dimethyl-4-chloropyrimidine, 2-chlorobenzthiazole or 4-chloroquinoline.

The products of the present invention are more or less viscous oils, which can be converted into salts which dissolve

well in water, and among which salts the phosphates have been found to be especially useful. The products exhibit excellent antispasmodic properties which are especially pronounced in the case of histamine spasms. There come into consideration more especially 1-phenyl-1-thiazole-(2')-3-dimethyl - aminopropane and 1 - phenyl - 1 - [2':6' - dimethyl-pyrimidyl-(4')]-3-dimethylamino-propane of the formula



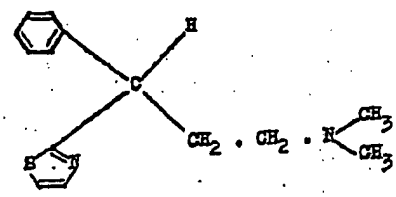
which boils at 122—126° C. under a pressure of 0.1 mm.

The following Examples illustrate the invention, the parts being by weight:—

EXAMPLE 1.

94 parts of α-phenyl-γ-dimethylamino-butyric acid nitrile are heated for 1 hour at 80° C. together with 200 parts of toluene and 22 parts of sodamide. After cooling, 60 parts of 2-chlorothiazole are added, and the product of the reaction is heated for 2 hours at 110° C. After decomposing the reaction product with water and separating the organic solution, there is obtained by fractional distillation, after a small quantity of first runnings, α-phenyl-α-thiazolyl - (2) - γ - dimethyl-amino-butyric acid nitrile boiling at 150—153° C. under a pressure of 0.25 mm. in a very good yield.

By heating the product for 2 hours with an excess of an alcoholic solution of potassium hydroxide, 1 - phenyl - 1-thiazolyl-(2')-3-dimethylamino-propane of the formula

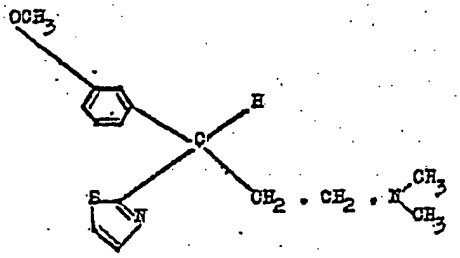


boiling at 136—138° C. under a pressure of 0.6 mm. is obtained in a very good yield. The phosphate containing two molecular proportions of water of crystallisation melts at 78—80° C.

EXAMPLE 2.

65.4 parts of α-(3-methoxyphenyl)-γ-dimethyl-amino-butyric acid nitrile (prepared from 3-methoxy benzyl cyanide, β - chlorethyl - dimethylamine and sodamide), 150 parts of toluene and 12.5 parts of sodamide are reacted with 36 parts of 2-chlorothiazole, and the product is heated for 1½ hours at about 110° C. The product is decomposed with water and subjected to a fractional distillation. α - (3 - Methoxy phenyl) - α - thiazolyl-(2)-γ-dimethylammino-butyric acid nitrile distils in good yield at a temperature of 155—160° C. under a pressure of 0.15 mm. in the form of a highly viscous yellow oil.

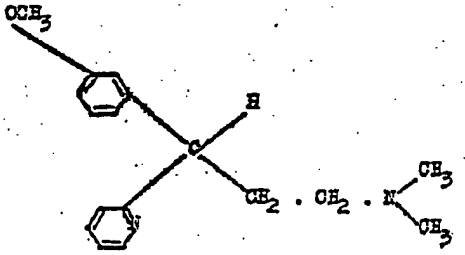
The nitrile group is then eliminated by treatment with an alcoholic solution of potassium hydroxide as described in Example 1 and there is obtained 1-(3'-methoxyphenyl) - 1 - thiazolyl - (2') - 3-dimethylaminopropane of the formula



boiling at 150—154° C. under a pressure of 0.5 mm.

EXAMPLE 3.

32.5 parts of α-(3-methoxyphenyl-γ-dimethylamino-butyric acid nitrile, 100 parts of toluene and 6 parts of sodamide are reacted with 17 parts of 2-chlorpyridine. By fractional distillation of the reaction product α-(3-methoxyphenyl)-α-pyridyl-(2)-γ-dimethylamino-butyric acid nitrile is obtained in a good yield, in addition to unchanged starting material. The product so obtained is a viscous reddish oil boiling at 168—170° C. under a pressure of 0.3 mm., from which, by eliminating the nitrile group in the manner described in Example 1, there is readily obtained the corresponding propane of the formula

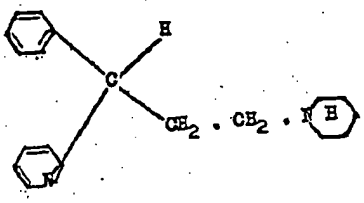


which boils at 155—160° C. under a pressure of 0.5 mm.

EXAMPLE 4.

13 parts of sodamide are introduced at 25—35° C. into a solution of 58.3 parts of phenyl - pyridyl-(2)-acetonitrile in 200 parts of benzene. The mixture is heated for a short time at 60—70° C. It is then cooled, and 48.5 parts of piperidino-ethyl chloride (boiling at 68—70° C. under a pressure of 12 mm.) are introduced dropwise. On heating to 50—60° C. the reaction sets in. Finally the reaction product is heated for 1 hour to 80° C., decomposed with water, and the benzene solution is separated. After a small amount of first runnings has distilled, α-phenyl-α-pyridyl-(2) - γ - (N-piperidino)-butyric acid nitrile distils at 185—190° C. under a pressure of 0.4 mm. in a yield of 90—95 per cent. in the form of a red viscous oil.

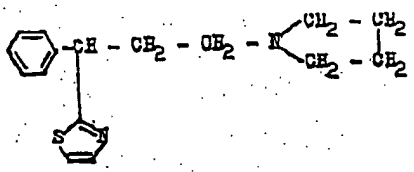
By treatment with an alcoholic solution of alkali 1-phenyl-1-pyridyl-(2')-3-piperidino-propane of the formula



is obtained in a very good yield in the form of a slightly coloured viscous oil boiling at 160—164° C. under a pressure of 0.25 mm.

EXAMPLE 5.

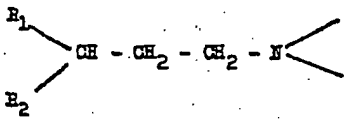
48 parts of α-phenyl-γ-N-pyrrolidino-butyric acid nitrile, boiling under a pressure of 0.1—0.2 mm. at 130—134° C., are heated for 30 minutes at 70—80° C. with 9.3 parts of sodamide in 200 parts of toluene, and, after cooling, gradually mixed with 27 parts of 2-chloro-thiazole at a temperature of 25—40° C. The mixture is heated for one hour at 90—95° C., mixed with 150 cc. of water, the toluene solution is separated and fractionally distilled. In addition to unchanged starting materials, α-phenyl-α-thiazolyl-(2)-γ-N-pyrrolidino-butyric acid nitrile is obtained as a viscous yellow oil boiling at 165—168° C. under a pressure of 0.15 mm. and melting at 83—85° C. 25 parts of this nitrile are boiled under reflux on the steam bath for 4 hours with 10 parts of caustic soda, 100 parts of ethyl alcohol and 10 parts of water. By working up in the usual manner 1-phenyl-1-thiazolyl-(2') - 3 - N - pyrrolidino - propane of the formula



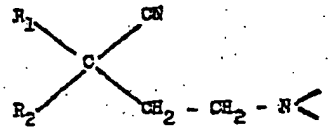
is obtained boiling at 136—139° C. under a pressure of 0.1 mm.

What we claim is:—

1. A process for the manufacture of the basic compounds of the general formula



in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula

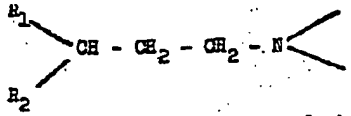


in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

2. A process as claimed in claim 1, wherein the alkali hydroxide is potassium hydroxide.

3. A process for the manufacture of the basic compound of any one of the Examples herein conducted substantially as described in that Example.

4. Basic compounds of the general formula

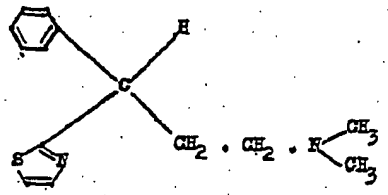


in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, when obtained by the process claimed in any one of claims 1—3.

5. Basic compounds as claimed in claim 4, wherein N< represents a dialkylamino group.

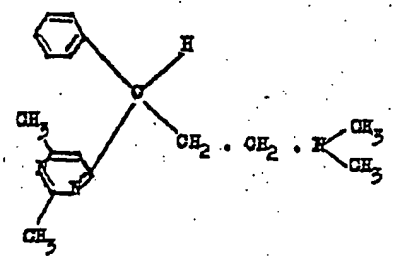
6. Basic compounds as claimed in claim 4, wherein N< represents a heterocyclic amino group.

7. 1 - Phenyl - 1 - thiazolyl-(2')-3-dimethylaminopropane of the formula



boiling at 136—138° C. under a pressure of 0.6 mm., when obtained by the process claimed in any one of claims 1—3.

8. 1 - Phenyl - 1 - [2':6' - dimethylpyrimidyl-(4')] - 3 - dimethylaminopropane of the formula



boiling at 122—126° C. under a pressure of 0.1 mm., when obtained by the process claimed in claim 1 or 2.

9. Any one of the basic compounds specified as end products of Examples 2—5 when obtained by the method substantially as described in that Example.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2. from which copies may be obtained.

Erteilt auf Grund der VO. vom 12. 5. 1943 – RGBl. II S. 150

AUSGEGEBEN AM
22. DEZEMBER 1952

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PATENTSCHRIFT

№ 766 207

KLASSE 12p GRUPPE 101

I 67372 IVc/12p

Nachträglich gedruckt durch das Deutsche Patentamt in München

(§ 20 des Ersten Gesetzes zur Änderung und Überleitung von Vorschriften auf dem Gebiet des gewerblichen Rechtsschutzes vom 8. Juli 1949)

Dr. Max Bockmühl, Dr. Gustav Ehrhart, Frankfurt/Main,
Dr. Otto Eisleb, Hofheim und Dr. Leonhardt Stein, Bad Soden (Taunus)
sind als Erfinder genannt worden

I. G. Farbenindustrie A. G., Frankfurt/Main

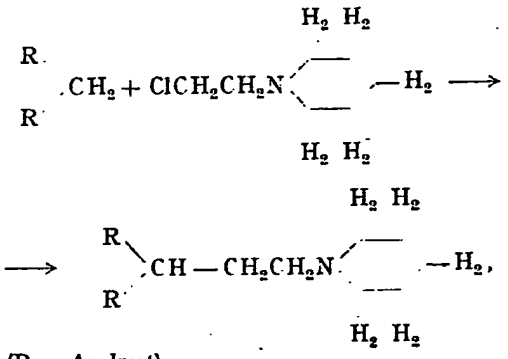
Verfahren zur Herstellung von basischen Verbindungen der Diarylmethanreihe

Patentiert im Deutschen Reich vom 9. Juli 1940 an
Der Zeitraum vom 8. Mai 1945 bis einschließlich 7. Mai 1950 wird auf die Patentdauer nicht angerechnet (Ges. v. 15. 7. 51)
Patenterteilung bekanntgemacht am 16. Oktober 1952

Es wurde gefunden, daß man zu basischen Verbindungen der Diarylmethanreihe, deren Arylreste auch untereinander verbunden sein können und die an dem die Arylreste tragenden Methankohlenstoff basische Alkylreste mit mindestens 2 C-Atomen in gerader Kette enthalten, auf folgende Weise gelangen kann:

Man kann ein Diarylmethan mit einem Aminoalkylhalogenid, dessen Aminogruppe durch Alkylgruppen substituiert sein kann, dessen halogentragende Alkylgruppe mindestens 2 C-Atome in gerader Kette enthält und in welchem zwei Alkylgruppen durch Brückenbindung miteinander verknüpft sein können, unter Verwendung halogenwasserstoffabspaltender Mittel umsetzen. Zum Beispiel erhält man durch Umsetzung von Diäthylaminoäthyl- oder Piperidinoäthylchlorid mit Diphenylmethan unter Verwendung von Natrium, Natriumamid, Phenylnatrium oder einer

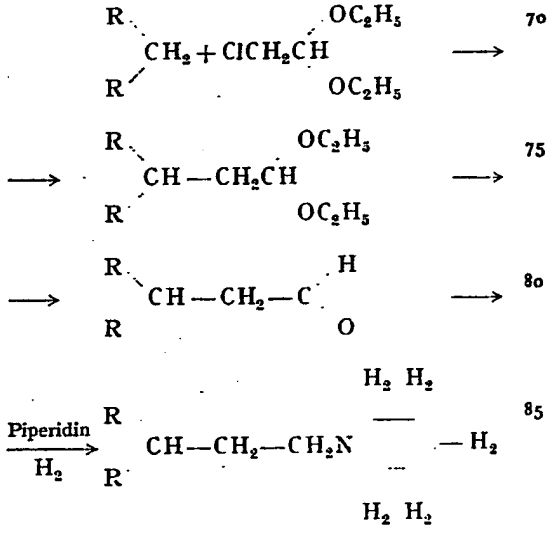
anderen geeigneten Alkaliverbindung als Halogenwasserstoffabspalter Diphenyldiäthylaminopropan bzw. Diphenylpiperidinopropan.



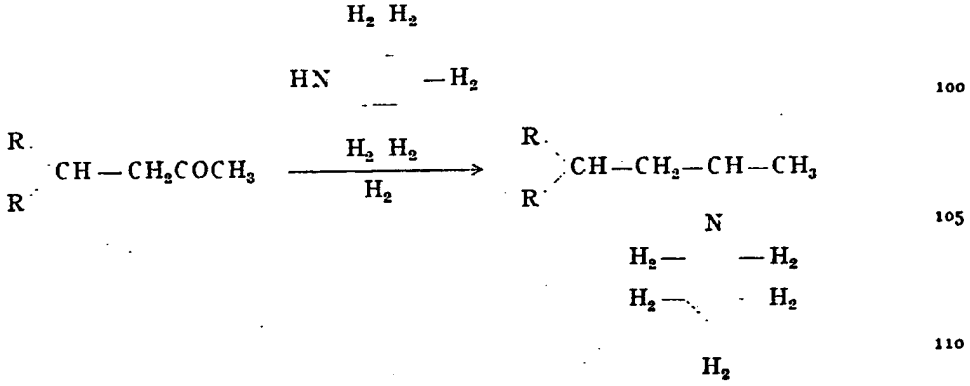
(R = Arylrest).

Ebenso lassen sich basische Alkylhalogenide mit verzweigter Kohlenstoffkette oder geeignete basische heterocyclische Halogenide, die obiger Definition entsprechen, verwenden, z. B. N-Methyl-β-halogenpiperidine. Auch läßt sich das Verfahren mit Diarylmethanen ausführen, deren Aryle miteinander verbunden sind, z. B. mit Fluoren.

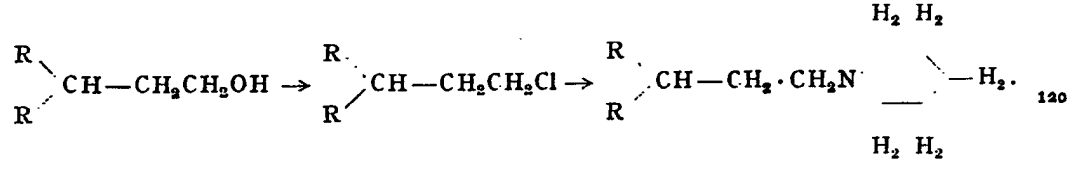
Man kann auch Diarylmethane, an deren Methankohlenstoff ein in geeignetem Abstand carbonylhaltiger Alkylrest steht, in Gegenwart von Ammoniak oder Aminen hydrieren. Zum Beispiel erhält man durch Einwirkung von Chloracetaldehydacetal auf Diphenylmethan unter Verwendung von Halogenwasserstoffabspaltern Diphenylpropionaldehydacetal, das sich durch Hydrolyse in den zugehörigen Aldehyd überführen läßt. Dieser gibt bei Hydrierung in Gegenwart von Ammoniak, primären oder sekundären Aminen die entsprechenden Diphenylpropylaminverbindungen.



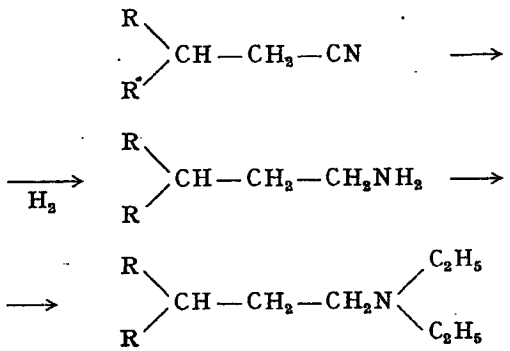
Geht man von Diphenyläthylmethylketon (Benzhydrylaceton) aus, so gelangt man beispielsweise durch Hydrierung in Gegenwart von Piperidin zu 2. 2-Diphenylpiperidinobutan.



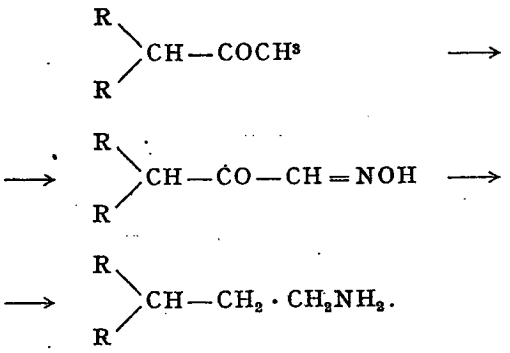
Ferner kann man geeignete Halogenalkyldiarylmethane mit Ammoniak oder Aminen umsetzen. Man führt beispielsweise Diphenylmethan vermittels Äthylenchlorhydrin in den Diphenylpropylalkohol über, wandelt diesen in das zugehörige Chlorid und letzteres vermittels Basen in die Diphenylpropylaminverbindungen um.



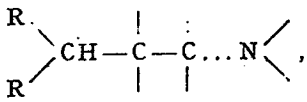
Auch kann man von einer nitrilhaltigen Diphenylmethanverbindung ausgehen, wie dem β,β-Diphenylpropionsäurenitril, welches man katalytisch zum Amin hydriert, worauf man gegebenenfalls die erhaltene Aminoverbindung alkyliert.



Endlich kann man Diaryl-alkylketone in die Isonitrosoverbindungen und letztere durch Reduktion in die zugehörigen Amine überführen, die gegebenenfalls noch alkyliert werden können. So kann man 1, 1-Diphenylaceton zum Diphenylisonitrosoketon nitrosieren, das sich durch Reduktion in das zugehörige Alkamin bzw. Amin überführen läßt.



Die Verfahrensprodukte bilden wasserlösliche Salze und zeigen sehr gute krampflösende Eigenschaften. Sie sollen daher als Arzneimittel oder zum Aufbau neuer Arzneistoffe verwendet werden. Sie besitzen die allgemeine Formel



in welcher also das Methankohlenstoffatom mit dem Stickstoffatom durch eine gerade Kette von mindestens 2 C-Atomen verbunden ist und diese Kette außerdem auch verzweigt sein kann.

Beispiele

1. Zu 101 g feingeschnittenem Natriumdraht in 100 ccm Benzol läßt man unter Rühren eine Mischung von 336 g Diphenylmethan und 235 g Chlorbenzol eintropfen. Die Temperatur wird zweckmäßig durch schwaches Kühlen auf etwa 35° gehalten. Nach etwa 7 bis 8 Stunden ist die Reaktion beendet. Dann läßt man ebenfalls bei 35° 240 g Piperidinoäthylchlorid eintropfen, rührt 1 Stunde bei Zimmertemperatur und kocht schließlich 1 Stunde unter Rückfluß. Die erkaltete Reaktionsmasse wird mit Wasser versetzt. Die benzolische Schicht wird abgetrennt und mit verdünnter Salzsäure ausgeschüttelt. Beim Alkalischmachen der sauren Lösung scheidet sich das α,α-Diphenyl-γ-piperidinopropan als Öl ab, welches unter 8 mm Druck bei 210 bis 220° siedet. Zur Darstellung des Chlorhydrats löst man die Base in Äther und säuert mit alkoholischer Salzsäure schwach an, wobei das zuerst ölig abgeschiedene Chlorhydrat sehr bald kristallinisch erstarrt. Durch Umkristallisieren aus Alkohol und Äther erhält man farblose Kristalle, die bei 214 bis 215° schmelzen.

2. Zu 11 g feingeschnittenem Natriumdraht in 100 ccm Benzol gibt man unter Rühren eine Mischung von 27 g Chlorbenzol und 34 g Diphenylmethan. Die Temperatur wird etwa 7 Stunden lang auf 35 bis 40° gehalten. Dann läßt man 21 g Morpholinoäthylchlorid unter schwacher Kühlung bei etwa 30 bis 35° eintropfen, rührt 1 Stunde bei Zimmertemperatur und kocht dann schließlich noch 1 Stunde unter Rückfluß. Man arbeitet wie im Beispiel 1 auf und erhält das α,α-Diphenyl-δ-morpholinopropan, welches unter 8 mm Druck bei 210 bis 220° siedet. Das Chlorhydrat bildet farblose Kristalle vom Schmelzpunkt 205 bis 206°.

3. Zu 10 g feingeschnittenem Natriumdraht in 100 ccm Benzol läßt man 25 g Chlorbenzol zutropfen. Die Temperatur steigt sehr bald und wird durch schwaches Kühlen auf 35° gehalten. Nach 2 Stunden ist die Reaktion beendet. Dann läßt man eine Lösung von 33 g Fluoren in 100 ccm Benzol zufließen, wobei nur geringe Temperaturerhöhung eintritt. Nach einstündigem Rühren bei Zimmertemperatur läßt man unter Kühlung 24 g Piperidinoäthylchlorid eintropfen. Zur Vervollständigung der Reaktion läßt man 1 Stunde bei Zimmertemperatur nachrühren und dann noch 1 Stunde unter Rückfluß kochen. Man erhält das α-Diphenylen-γ-piperidinopropan vom Kp. 230 bis 240° bei 7 mm Druck. Das Chlorhydrat schmilzt bei 205°.

4. Zu 5,5 g feingeschnittenem Natriumdraht in 50 ccm Benzol läßt man unter Rüh-

ren ein Gemisch von 13,5 g Chlorbenzol und 17 g Diphenylmethan eintropfen. Die Temperatur hält man 7 bis 8 Stunden lang auf 35 bis 40°. Dann läßt man bei 35° eine Lösung von 20 g 1, 3-Piperidinopropylbromid in 50 ccm Benzol eintropfen und kocht zur Vervollständigung der Reaktion noch 1 Stunde unter Rückfluß. Das erhaltene α, α-Diphenyl-δ-piperidinobutan siedet unter 8 mm Druck bei 225 bis 235°. Sein Chlorhydrat schmilzt bei 171°.

5. Zu 11 g feingeschnittenem Natriumdraht in 50 ccm Benzol läßt man unter Rühren ein Gemisch von 27 g Chlorbenzol und 34 g Diphenylmethan zutropfen. Man verfährt wie oben und läßt dann bei 35° 30 g α-Piperidino-β-chlorpropan zutropfen. Man erhält das α, α-Diphenyl-β-methyl-γ-piperidinopropan vom Kp. 220 bis 230° bei 13 mm Druck. Schmelzpunkt des Chlorhydrats 211 bis 212°.

6. Aus Diphenylmethan und N-Methyl-3-chlorpiperidin erhält man unter den gleichen Bedingungen das Diphenyl-[N-methylpiperidyl-(3)]-methan, welches unter 8 mm Druck bei 195 bis 200° siedet. Das Chlorhydrat schmilzt unscharf bei 110 bis 120° unter Zersetzung.

7. 67,2 g Diphenylmethan geben mit 60 g Chloracetaldehydacetal in benzolischer Lösung unter Verwendung von 20 g Natrium und 50 g Chlorbenzol das Diphenylpropionaldehydacetal, das durch einstündiges Erhitzen auf dem Dampfbad mit 100 ccm 2 n-Schwefelsäure unter Umschütteln in den freien Aldehyd übergeführt wird. Der Siedepunkt des Aldehyds ist 190 bis 200° bei 13 mm Druck. Zur Überführung des Aldehyds in das Amin werden 5,6 g Aldehyd in Gegenwart von 3 g Piperidin in alkoholischer Lösung und von Nickel als Katalysator hydriert. Das Hydrierungsprodukt wird wie üblich aufgearbeitet und stellt das α, α-Diphenyl-γ-piperidinopropan dar.

8. 84 g Diphenylmethan geben mit 61 g Essigsäurechloräthylester unter Verwendung von Chlorbenzol und Natrium den Essigsäure-1, 1-diphenylpropylester-(3), der bei 200° und 18 mm Druck destilliert. Zum Verseifen der Acetylverbindung werden 14 g Ester mit 40 ccm Alkohol und 20 g Ätzkali 2 Stunden auf dem Dampfbad erhitzt. Nach dem Abkühlen wird mit Wasser verdünnt, ausgeäthert und der Ätherrückstand im Vakuum abdestilliert. Das Diphenylpropanol, das auch durch Reduktion von β, β-Diphenylpropionsäureester mit Na und Alkohol gewonnen werden kann, siedet unter 18 mm Druck zwischen 180 und 190°. Zur Überführung in das Chlorid werden 10 g Diphenylpropanol mit 25 ccm Benzol und 10 g Thionylchlorid 2 Stunden auf dem Dampfbad gekocht. Das erhaltene Chlorid wird nach Entfernen der flüchtigen Stoffe mit 10 g Piperidin auf dem Dampfbad umgesetzt. Nach Aufarbeiten des Reaktionsproduktes erhält man das α, α-Diphenyl-γ-piperidinopropan.

9. 77 Gewichtsteile Diphenylmethan, 77 Gewichtsteile Toluol, 65 Gewichtsteile β-Chloräthyldiäthylamin und 20 Gewichtsteile fein pulverisiertes Natriumamid werden zusammen 6 Stunden unter Rückfluß gekocht. Nach dem Erkalten wird zur Auflösung des ausgeschiedenen Natriumchlorids Wasser zugesetzt; der abgetrennten Toluollösung wird die Base durch Ausschütteln mit verdünnter Salzsäure entzogen. Sie wird daraus mit Natronlauge als Öl abgeschieden, in Äther aufgenommen, abgetrennt und nach dem Trocknen über Kaliumcarbonat destilliert. Kp_4 170 bis 175°. Die Base, nämlich α, α-Diphenyl-γ-diäthylaminopropan, ist ein farbloses Öl. Das Hydrochlorid, aus der Base in Äther mit alkoholischer Salzsäure bereitet, ist ein farbloses Kristallpulver, das bei 143 bis 144° schmilzt.

10. 46 Gewichtsteile Fluoren, 80 Gewichtsteile Toluol, 37 Gewichtsteile β-Chloräthyldiäthylamin und 11 Gewichtsteile fein pulverisiertes Natriumamid werden zusammen unter Rühren erhitzt. Ab 60° beginnt die Reaktion. Das Gemisch wird langsam bis auf 105° erhitzt und 4 Stunden dabei gehalten. Nach dem Abkühlen wird verdünnte Salzsäure bis zur congosauren Reaktion zugesetzt. Aus der abgetrennten wäßrigen Salzlösung wird mit Natronlauge die Base gefällt, die unter 4 mm Druck bei 192 bis 210° als farbloses dickes Öl destilliert. Das Diäthylaminoäthylfluoren bildet ein gut kristallisierendes saures Sulfat, das sich aus Alkohol umkristallisieren läßt und in Wasser leicht löslich ist. Schmelzpunkt 217 bis 218°.

11. 13,7 g Benzhydrylaceton (Diphenyläthylmethylketon) werden in 200 ccm Alkohol mit 10 ccm 54%igem wäßrigem Methylamin in Gegenwart eines Nickelkatalysators bei 120° und 50 Atm. Druck mit Wasserstoff gerührt. Nach Beendigung der Wasserstoffaufnahme wird vom Nickel abgesaugt, der Alkohol abdestilliert und der Rückstand mit verdünnter Natronlauge und Äther behandelt. Die getrocknete ätherische Lösung wird mit ätherischer Salzsäure angesäuert, wobei sich sofort das α, α-Diphenyl-γ-methylaminobutanchlorhydrat abscheidet. Nach dem Umlösen aus Alkohol und Essigester erhält man farblose Prismen vom Schmelzpunkt 170 bis 172°.

12. Aus molekularen Mengen Diphenylmethan und Dimethylaminoäthylchlorid erhält man gemäß Beispiel 9 unter Verwendung von Natriumamid als halogenwasserstoffabspaltendem Mittel das α, α-Diphenyl-γ-dimethylaminopropan. Siedepunkt der Base 170

bis 173° unter 10 mm Druck. Das Chlorhydrat zeigt den Schmelzpunkt 168°.

13. Aus molekularen Mengen Diphenylmethan und Pyrrolidinoäthylchlorid (Kp_{35} 80 bis 81°) erhält man unter Verwendung von Natriumamid das α, α-Diphenyl-γ-pyrrolidinopropan vom Siedepunkt 190 bis 192° bei 4 mm Druck. Das primäre Phosphat schmilzt bei 160 bis 161°.

14. 19 g Benzhydrylaceton und 19 g Piperidin werden in alkoholischer Lösung in Gegenwart eines Nickelkatalysators bei 125° und etwa 50 atü hydriert. Das entstandene α, α-Diphenyl-γ-piperidinobutan zeigt den Siedepunkt 200 bis 203° unter 6 mm Druck. F. des Chlorhydrates 214°.

15. 11,9 g Natrium in 50 ccm Benzol und 29 g Chlorbenzol werden mit 43,3 g Diphenylmethan umgesetzt und dann mit 29 g 1-Chlor-2-piperidinopropan, dargestellt aus α-Brompropionsäureäthylester gemäß Helv. Chim. Acta Bd. 5, S. 476, umgesetzt. Das α, α-Diphenyl-γ-piperidinobutan siedet bei etwa 205° unter 6 mm Druck. Die Verbindung ist identisch mit der nach Beispiel 14 erhaltenen.

PATENTANSPRUCH:

Verfahren zur Herstellung von basischen Verbindungen der Diarylmethanreihe, deren Arylreste auch untereinander verbunden sein können und die im Methankohlenstoff basische Alkylreste von mindestens 2 Kohlenstoffatomen in gerader Kette enthalten, dadurch gekennzeichnet, daß man Diarylmethane mit Aminoalkylhalogeniden, deren Aminogruppe durch Alkylgruppen substituiert sein kann, deren halogentragende Alkylgruppe mindestens 2 C-Atome in gerader Kette enthält und in welchen zwei Alkylgruppen durch Brückenbindung miteinander verknüpft sein können, unter Verwendung von halogenwasserstoffabspaltenden Mitteln kondensiert; oder daß man Diarylmethane, an deren Methankohlenstoff ein in geeignetem Abstand carbonylhaltiger Alkylrest steht, in Gegenwart von Ammoniak, primären oder sekundären Basen hydriert; oder daß man Diarylalkylketone in die Isonitrosoverbindungen und letztere durch Reduktion in die zugehörigen Amine überführt und diese gegebenenfalls alkyliert; oder daß man geeignete Halogenalkyldiarylmethane mit Ammoniak oder Aminen umsetzt; oder daß man Diarylalkylmethane, die im aliphatischen Rest eine Nitrilgruppe enthalten, reduziert und die so erhaltenen Amine gegebenenfalls alkyliert.

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METHOD FOR PREPARING BASIC COMPOUNDS OF THE DIARYLMETHANE SERIES

(German Patent No. 766 207)

It was found that one may arrive at basic compounds of the diarylmethane series, whose aryl groups may also be combined among one another, and which, at the methane carbon carrying the aryl groups, contain basic alkyl groups having at least two C atoms in a straight chain, in the following way:

One may react a diarylmethane with an aminoalkylhalogenide, whose amino group may be substituted by alkyl groups, whose halogen-bearing alkyl group contains at least 2 C atoms in a straight chain, and in which two alkyl groups may be linked to each other by bridging, while using halogenhydrogen-splitting **[eliminating]** means. For instance, by reacting diethylaminoethyl chloride or piperidinoethyl chloride with diphenylmethane while using sodium, sodium amide, phenyl sodium or another suitable alkali compound as halogenhydrogen eliminator, one obtains diphenyldiethyl aminopropane or diphenylpiperidinopropane.

[see first equation in the original, page 2, left column, (Arylrest = aryl group)]]

In the same way, basic alkylhalogenides, having a branched carbon chain, or suitable basic heterocyclic halogenides, which correspond to the above definition, may be used, for instance, N-methyl-β-halogenpiperidine. The method may also be carried out

using diarylmethanes whose aryls are combined with one another, for instance, with fluorene.

It is also possible to hydrogenate diarylmethane, on whose methane carbon there is a carbonyl-containing alkyl group at a suitable distance, in the presence of ammonia or amines. For instance, by the action of chloroacetaldehydeacetal on diphelymethane using halogenhydrogen eliminators, one obtains diphenylpropionaldehydeacetal, which may be converted to the pertaining aldehyde by hydrolysis. The latter, by hydrogenation in the presence of ammonia, primary or secondary amines yields the corresponding diphenylpropylamine compounds.

[see equation in the original, page 2, upper right column]

Starting with diphelyethylmethyl ketone (benzohydrylacetone), using hydrogenation in the presence of piperidine, yields α,α-diphenylpiperidinobutane.

[see equation in the original, across page 2, upper]

One may also react suitable halogenalkyldiarylmethanes with ammonia or amines. For example, one may convert diphenylmethane into diphenylpropyl alcohol using ethylenechlorohydrin, convert this to the appertaining chloride, and convert the latter to diphenylpropylamino compounds by means of bases.

[see equation in the original, across page 2, lower]

One may also begin with a nitrile-containing diphenylmethane compound, such as β,β-diphenylpropionic acid nitrile, which is hydrogenated catalytically to the amine, whereupon, if desired, the amino compound obtained is alkylated.

[see equation in the original, page 3, top]

Finally, one may convert diaryl-alkylketones to isonitroso compounds, and the latter to the appertaining amine by reduction, and the amines, if desired, may still be alkylated. Thus one may nitrosate 1,1-diphenylacetone to diphenylisonitrosoketone, which may be converted by reduction to the appertaining alcamine or amine.

[see equation in the original, page 2, middle]

The method products form water-soluble salts, and demonstrate very good spasmolytic properties. They should therefore be used as remedies or for the synthesis of new remedial substances. They have the general formula

[see formula in the original, page 2, bottom]

in which, thus, the methane carbon atom is connected to the nitrogen atom by a straight chain of at least two C atoms, and this chain may be branched as well.

EXAMPLES

1. A mixture of 336 g diphenylmethan and 235 g chlorobenzene is dripped into 101 g finely cut sodium wire in 100 cc benzene while stirring. The temperature is expediently held to about 35° by slight cooling. After about 7 to 8 hours the reaction is finished. Then, also at 35°, 240 g piperidinoethyl chloride is dripped in, the mixture is stirred for 1 hour at room temperature and is finally boiled for 1 hour under reflux. The cooled reaction product is laced with water. The benzene layer is separated and extracted with dilute hydrochloric acid. When the acid solution is made alkaline, the α,α-diphenyl-γ-piperidinopropane separates out as an oil, which boils under 8 mm pressure at 210 to 220°. For the preparation of the chlorohydrate, the base is dissolved in ether and this is then made slightly acid using alcoholic hydrochloric acid, whereupon the chlorohydrate, which first separates as an oil, very soon solidifies as crystals. By recrystallizing from alcohol and ether, colorless crystals are obtained which melt at 214 to 215°.

2. A mixture of 27 g chlorobenzene and 34 g diphenylmethane is dripped into 11 g finely cut sodium wire in 100 cc benzene while stirring. The temperature is held to 35°-40° for about 7 hours. Then, at about 30-35°, 21 g morpholinoethyl chloride is dripped in under slight cooling, the mixture is stirred for 1 hour at room temperature and is finally boiled for 1 hour under reflux. The mixture is worked up as in example 1, and this yields α,α-

diphenyl-δ-morpholinopropane, which boils at 210 to 220° under 8 mm of pressure. The chlorohydrate forms colorless crystals having a melting point of 205 to 206°.

3. 25 g chlorobenzene are dripped into 10 g finely cut sodium wire in 100 cc benzene. The temperature rises very quickly, and is held to 35° by slight cooling. The reaction is over after 2 hours. Then a solution of 33 g fluorene in 100 cc benzene is allowed to flow in, whereupon only a slight temperature increase takes place. After stirring for one hour at room temperature, 24 g piperidinoethyl chloride are dripped in under cooling. To complete the reaction, stirring is continued for 1 hour at room temperature and then boiling for 1 hour under reflux. The yield is α-diphenylene-γ-piperidinopropane, having a boiling point of 230 to 240° at 7 mm of pressure. The chlorohydrate melts at 205°.

4. A mixture of 13.5 g chlorobenzene and 17 g diphenylmethane is dripped into 5.5 g finely cut sodium wire in 50 cc benzene while stirring. The temperature is held to 35 to 40° for 7 to 8 hours. Then a solution of 1,3- piperidinopropyl bromide in 50 cc benzene is dripped in, and the mixture is boiled for 1 hour under reflux to complete the reaction. The α,α-diphenyl-δ-piperidinobutane obtained boils at 225-235° under 8 mm of pressure. Its chlorohydrate melts at 171°.

5. A mixture of 27 g chlorobenzene and 34 g diphenylmethan is dripped into 11 g finely cut sodium wire in 50 cc benzene while stirring. Proceed as above, and then, at 35°, 30 g α-piperidino-β-chloropropane are dripped in. This yields α,α-diphenyl-β-methyl-γ-piperidinopropane, boiling point 220 to 230° at 13 mm of pressure. The melting point of the chlorohydrate is 211 to 212°.

6. From diphenylmethane and N-methyl-3-chloropiperidine one obtains, under the same conditions, diphenyl-[N-methylpiperidyl-(3)]-methane, which boils at 195 to 200°. The chlorohydrate melts imprecisely at 110 to 120° with decomposition.

7. Diphenylpropionaldehydeacetal is produced by 67.2 g diphenylmethane and 60 g chloroacetaldehydeacetal in benzene solution, using 20 g sodium and 50 g chlorobenzene, and it is converted to the free aldehyde by heating on a steambath for 1 hour with 100 cc 2 n-sulfuric acid while shaking. The boiling point of the aldehyde is 190 to 200° at 13 mm of pressure. In order to covert the aldehyde into the amine, 5.6 g aldehyde are hydrogenated in the presence of 3 g piperidine in alcoholic solution and in the presence of nickel as catalyst. The hydrogenated product is worked up as usual and yields α,α-diphenyl-γ-piperidinopropane.

8. Acetic acid chloroethyl ester-(3) is produced by 84 g diphenylmethane and 61 g acetic acid chloroethyl ester using chlorobenzene and sodium, and it is distilled at 200° and 18 mm of pressure. In order to saponify the acetyl compound, 14 g ester are heated with 40 cc alcohol and 20 g potassium hydroxide for 2 hours on a steambath. After cooling, the mixture is diluted with water, extracted with ether, and the ether residue is distilled off in a vacuum. The diphenylpropanol, which can also be prepared by the reduction of β,β-diphenylpropionic acid ester using sodium and alcohol, boils between 180 to 190° under 18 mm of pressure. To convert to the chloride, 10 g diphenylpropanol with 25 cc benzene and 10 g thionyl chloride are boiled for 2 hours on a steambath. After removing the volatile substances, the chloride obtained is reacted with 10 g

piperidine on a steambath. After working up the reaction product, α,α-diphenyl-γ-piperidinopropane is obtained.

9. 77 parts by weight diphenylmethane, 77 parts by weight toluene, 65 parts by weight β-chloroethyldiethylamine and 20 parts by weight finely powdered sodium amide are boiled together for 6 hours under reflux. After cooling, water is added to dissolve the separated sodium chloride; the base is withdrawn from the separated toluene solution by extracting with dilute hydrochloric acid. From this it is forced out of solution as an oil, using sodium hydroxide solution, taken up in ether, separated, and after drying it is distilled over potassium carbonate. B.p. 170 to 175°. The base, namely, α,α-diphenyl-γ-diethylaminopropane, is a colorless oil. The hydrochloride, which is prepared from the base in ether, using alcoholic hydrochloric acid, is a colorless crystal powder, which melts at 143 to 144°.

10. 46 parts by weight fluorene, 80 parts by weight toluene, 37 parts by weight β-chloroethyldiethylamine and 11 parts by weight finely powdered sodium amide are heated together while stirring. The reaction begins at 60°. The mixture is heated slowly up to 100° and held there for 4 hours. After cooling, dilute hydrochloric acid is added to attain the congo acid reaction. From the separated aqueous salt solution, the base is brought down using sodium hydroxide solution, and it is distilled under 4 mm of pressure at 192 to 210° as a colorless thick oil. The diethylaminoethylfluorene forms a well crystallizing acid sulfate, which may be recrystallized from alcohol and is easily soluble in water. M.p. is 217 to 218°.

11. 13.7 benzohydrylacetone (diphenylethylmethylketone) are stirred in 200 cc alcohol with 10 cc of 54% aqueous methylamine in the presence of a nickel catalyst, at 120° and 50 atm. of pressure with hydrogen. After termination of the hydrogen absorption, the mixture is filtered off from the nickel, the alcohol is distilled off and the residue is treated with dilute sodium hydroxide solution and ether. The dried ethereal solution is made acid with ethereal hydrochloric acid, whereupon α,α-diphenyl-γ-methylaminobutane chlorohydrate comes out of solution. After redissolving from alcohol and ethyl acetate, colorless prisms are obtained having a melting point of 170 to 172°.

12. From molecular quantities of diphenylmethane and dimethylaminoethyl chloride, according to example 9 and using sodium amide as the halogenhydrogen splitting-off means, α,α-diphenyl-γ-dimethylaminopropane is obtained. Boiling point of the base is 170 to 173° under 10 mm of pressure. The chlorohydrate has a melting point of 168°.

13. From molecular quantities of diphenylmethane and pyrrolidinoethyl chloride ($b.p._{35}$ 80 to 81°) and using sodium amide α,α-diphenyl-γ-pyrrolidinopropane is obtained, having a boiling point 190 to 192° at 4 mm of pressure. The primary phosphate has a melting point of 160 to 161°.

14. 19 g benzohydrylacetone and 19 g piperidine are hydrogenated in an alcoholic solution in the presence of a nickel catalyst at 125° and approximately 50 atm. The α,α-diphenyl-γ-piperidinobutane created demonstrates a boiling point of 200 to 203° under 6 mm of pressure. Freezing point of the chlorohydrate is 214°.

15. 11.9 g sodium in 50 cc benzeneand 29 g chlorobenzene are reacted with 43.3 g diphenylmethane, and then reacted with 29 g 1-chloro-2-piperidinopropane, prepared from α-bromopropionic acid ethyl ester according to Helv. Chim. Acta vol. 5, page 476. The α,α-diphenyl-γ-piperidinobutane boils at about 205° under 6 mm of pressure. The compound is identical with the one obtained according to example 14.

What is claimed is:

A method for preparing basic compounds of the diarylmethane series, whose aryl groups may also be combined among one another, and which, at the methane carbon contain basic alkyl groups having at least 2 carbon atoms in a straight chain, wherein diarylmethane may be condensed with aminoalkylhalogenides, whose amino group may be substituted by alkyl groups, whose halogen-bearing alkyl group contains at least 2 C atoms in a straight chain, and in which two alkyl groups may be linked to each other by bridging, while using halogenhydrogen-splitting **[eliminating]** means; diarylmethane, on whose methane carbon there is a carbonyl-containing alkyl group at a suitable distance, may be hydrogenated in the presence of ammonia, primary or secondary bases; or diarylalkylketones may be converted to isonitroso compounds, and the latter to the appertaining amines by reduction, and the amines may be alkylated, if desired; or one may also react suitable halogenalkyldiarylmethanes with ammonia or amines; or one may reduce the diarylalkylmethanes, which contain a nitrile group in the aliphatic group, and alkylate the amines thus obtained, if desired.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 211/06, 215/54, 217/62, 237/30, 255/33, C07D 333/20, A61K 31/135, 31/33

A1

(11) International Publication Number: **WO 98/43942**

(43) International Publication Date: 8 October 1998 (08.10.98)

(21) International Application Number: PCT/SE98/00556

(22) International Filing Date: 26 March 1998 (26.03.98)

(30) Priority Data:
9701144-9 27 March 1997 (27.03.97) SE

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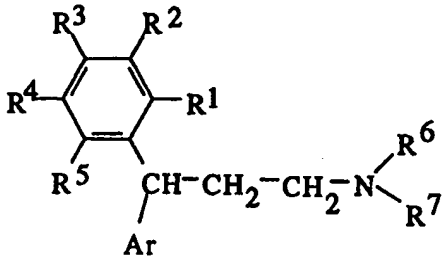
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS, THEIR USE AND PREPARATION

(57) Abstract

The invention relates to novel compounds of Formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. The compounds have anticholinergic activity, and the invention also relates to the compounds of Formula (I) for use as therapeutically active substances, pharmaceutical compositions containing compounds of Formula (I), the use of the compounds of Formula (I) for preparing anticholinergic drugs, the use of the compounds of Formula (I) for treating urinary incontinence, and methods for preparing the compounds of Formula (I).



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NOVEL COMPOUNDS, THEIR USE AND PREPARATION

TECHNICAL FIELD

The present invention relates to novel therapeutically active compounds, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

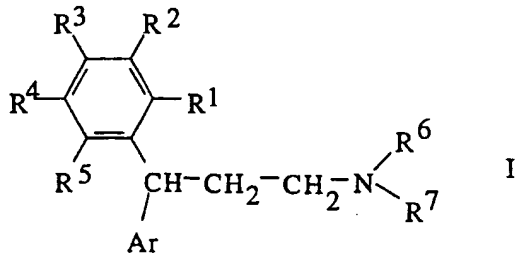
BACKGROUND OF THE INVENTION

WO 89/06644 and WO 94/11337 disclose tertiary 3,3-diphenylpropylamines having anticholinergic activity, especially for the treatment of urinary incontinence. SE-A-215499 discloses secondary 3,3-diphenylpropylamines having an advantageous effect on the heart and circulation. US-A-3,446,901, GB-A-1,169,944 and GB-A-1,169,945 disclose 3,3-diphenylpropylamines having antidepressant activity. DE-B1-1216318 discloses preparation of diphenylalkylamines having effect on the heart and circulation.

SUMMARY OF THE INVENTION

In accordance with the present invention, novel therapeutically active diarylpropylamines have been found which like the 3,3-diphenylpropylamines known from WO 89/06644 and WO 94/11337 above have favourable anticholinergic properties, and which therefore also can be used for the control of events mediated by acetylcholine, like urination.

In one aspect, the present invention provides novel compounds represented by the general formula I:



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,

R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl of at least two carbon atoms, alkoxy of at least two carbon atoms, hydroxyalkyl of at least two carbon atoms,

R^5 is hydrogen, halogen, alkyl,

Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and

R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen,

with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or

(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or

(iii) Ar is heteroaryl, or

(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then

R^4 may also be hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, halogen, carbamoyl, sulphamoyl;

and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;

their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

In another aspect, the present invention provides the compounds having the general Formula I above for therapeutical use, especially for the treatment of urinary incontinence related disorders.

In still another aspect, the present invention provides a pharmaceutical composition comprising one or more compounds of the general Formula I above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

In yet another aspect, the present invention provides a method of treating a patient (animals, including humans) suffering from a disorder related to urinary incontinence, which method comprises the step of administering to the said patient an effective amount of a compound having the general Formula I above.

In another aspect, the present invention provides the compounds according to Formula I for use as a pharmaceutically active substance, especially as an anticholinergic agent.

In yet another aspect, the present invention provides the use of the compounds having the general Formula I above for the manufacture of a medicament for the treatment of urinary incontinence related disorders.

In still another aspect, the present invention provides processes for preparing compounds having the general Formula I above.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises novel 3,3-diarylpropylamines and their pharmaceutically acceptable salts which are characterized by Formula I above and which

are useful as anticholinergic agents. The compounds are particularly useful for treatment of urinary incontinence.

One subgroup of compounds of Formula I is defined by the substituent R^4 being ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkyl-aminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyl-aminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

Another subgroup of the compounds of Formula I is defined by Ar being heteroaryl.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

Still another subgroup of the compounds of Formula I is defined by R^1 being hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen. Preferaby, Ar is then other than phenyl that is ortho-substituted by hydroxy or alkoxy.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

Yet another subgroup of the compounds of Formula I is defined by at least one of R^6 and R^7 being aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom at one or more positions.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

In the compounds of Formula I, "alkyl", separately and in combinations, is preferably C_{1-8}alkyl, i.e. methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof, more preferably C_{1-6}alkyl, especially C_{1-4}alkyl.

Similarly, "alkoxy", separately and in combinations, is preferably C_{1-8}alkoxy, i.e. methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy, and isomeric forms thereof, more preferably C_{1-6}alkoxy, especially C_{1-4}alkoxy.

"Aryl" means phenyl or naphthyl. "Heteroaryl" refers to a 5- or 6-membered heteroaromatic ring having from one to three heteroatoms, and which optionally may be fused to a homoaromatic ring, such as a benzene ring. Exemplary heteroaryl groups are morpholinyl, thienyl, furyl, piperazinyl, piperidinyl, imidazolinyl, pyridazolinyl, oxazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl.

"Halogen" includes fluoro, chloro, bromo and iodo.

When aryl is mono-substituted, it is preferably substituted in 2-position. When aryl is di-substituted, it is preferably substitued in positions 2 and 4. Preferred substituents are methyl, methoxy, hydroxy, hydroxymethyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

especially methyl, hydroxymethyl and halogen. Aryl is preferably phenyl.

Preferred heteroaryl groups are thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl and methylpyrryl.

R^1 is preferably hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

R^2 and R^3 are preferably selected from hydrogen, hydroxy and methoxy.

R^4 is preferably hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyl, amino, azido, cyanoalkyl, carboxy or carboxyalkyl. More preferably, R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethyl-aminoethyl.

R^5 is preferably hydrogen.

R^6 and R^7 independently of each other preferably signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group, such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms. R^6 and R^7 may carry one or more hydroxy groups and they may be joined to form a ring together with the nitrogen atom. It is preferred that at least one of R^6 and R^7 comprises a branched carbon chain.

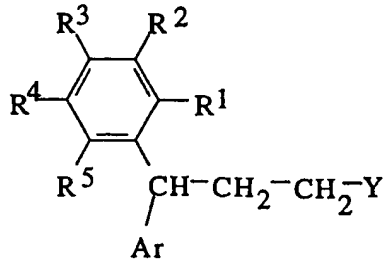
Exemplary groups $-NR^6,R^7$ are diethylamino, diisopropylamino, methyl-tert.-butylamino, methyl-tert.-pentylamino, piperidino, 2,2,6,6-tetramethylpiperidino, methylcyclobutylamino, methylcyclopentylamino, methylcyclohexylamino, methylcycloheptylamino, pyrrolidino, 2,2,5,5-tetramethylpyrrolidino, N-methyl-N-adamantylamino, especially diisopropylamino.

Representative compounds of Formula I are:
N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine, and its 3(R)-isomer
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxy-phenyl]-3-phenylpropanamine, and its 1(S*)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, and its (R)-isomer

The compounds of Formula I may, in accordance with the present invention, be prepared by per se conventional methods, and especially by

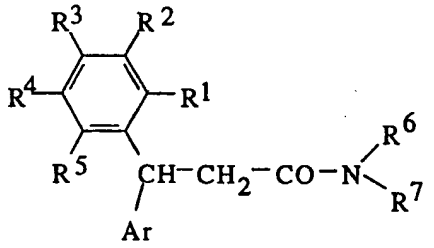
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined above for Formula I, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

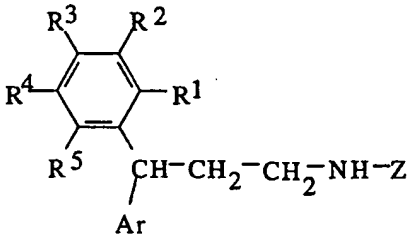
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, or

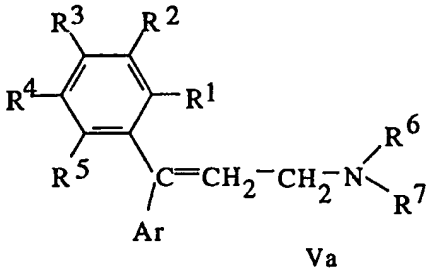
c) N-alkylating a secondary amine of Formula IV



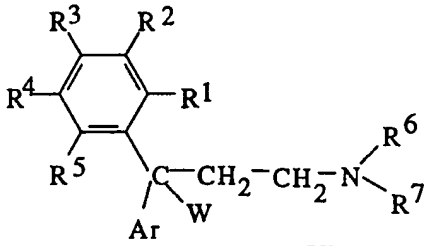
IV

wherein R^1 to R^5 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



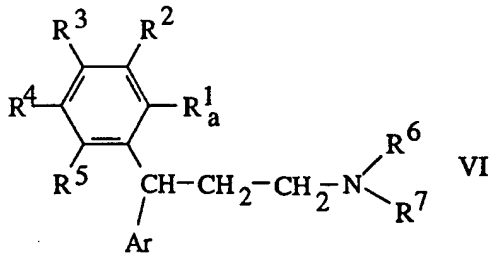
Va



Vb

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

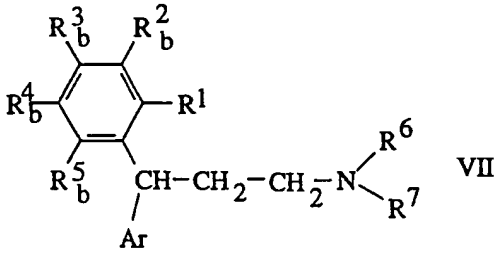
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined above for Formula I, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

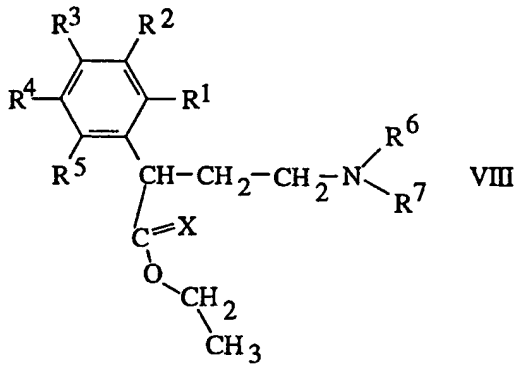


VII

wherein R^1, R^6, R^7 and Ar are as defined above for Formula I, and one of R^2b to R^5b is alkylene and the others are as defined above for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined above, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

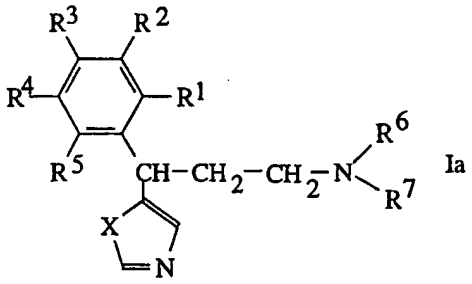


VIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, with a compound of Formula IX

$$CH_3N{=}C: \qquad \text{IX}$$

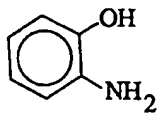
to form a compound of Formula Ia



Ia

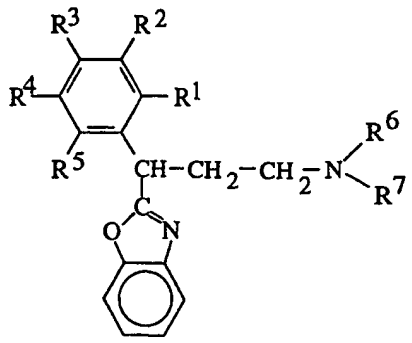
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

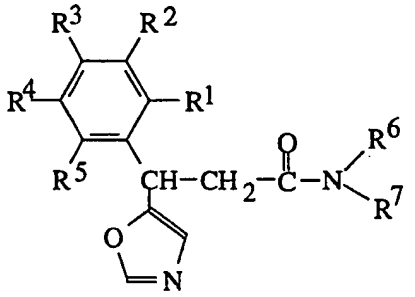
to form a compound of Formula Ib



Ib

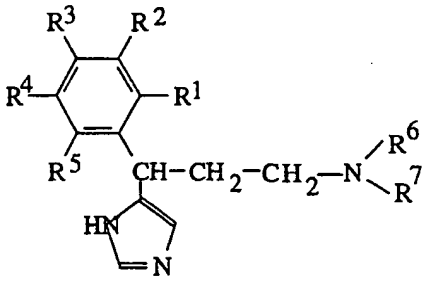
wherein R^1 to R^7 are as defined above for Formula I, or

j) converting a compound of Formula XI



XI

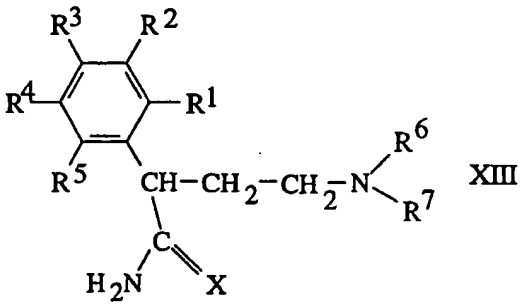
wherein R^1 to R^7 are as defined above for Formula I, to a compound of Formula XII



XII

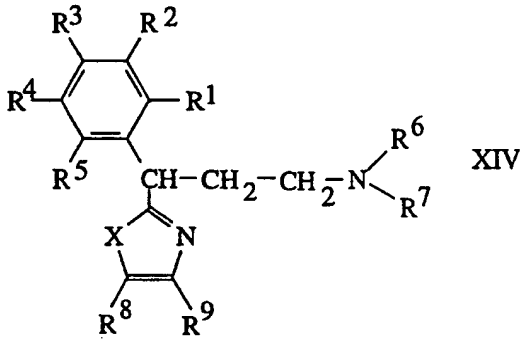
wherein R^1 to R^7 are as defined above for Formula I, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, to a compound of Formula XIV



XIV

wherein R^1 to R^7 and X are as defined above for Formula I, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,

ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

Appropriate reaction conditions in the above reactions may readily be selected by the skilled person with reference to analogous prior art methods and with due consideration of the specific Examples below. The necessary starting materials are either known or may be prepared in analogy with the preparation of known compounds.

The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallisation of salts with chiral acids or by chromatographic separation on chiral columns.

In accordance with the present invention, the compounds of Formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of Formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions can, as mentioned above, be used for the same therapeutical indications as the compounds of the above-mentioned WO 89/06644 or WO 94/11337, i.e. for the treatment of acetylcholine-mediated disorders, such as urinary incontinence, especially urge incontinence. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the

condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kilo of body weight, administered singly or multiply in doses e.g. from about 0,05 mg to about 200 mg each.

The invention will be further illustrated by the following non-limiting example and pharmacological tests.

General

N.M.R data were acquired on a Jeol JNM-EX 270 or a Varian Unity 500 spectrometer. Spectra were recorded with tetramethylsilane (TMS) as internal standard at 30°C. Infrared spectra were recorded on a Perkin-Elmer Model Model 841 spectrophotometer. Non-corrected melting points were obtained on a Koeffler apparatus. Gas chromatography was performed on a HP 5940 instrument with a 10 m HP-1 column and the oven heated in the linear temperature gradient mode. All lithium aluminum hydride reductions were quenched by the use of the procedure according to V. Micovic and M. Mihailovic (J. Org. Chem. 18, 1190 (1953)).

EXAMPLE 1

N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (2.75 g, 7 mmol) in THF (40 mL) was added to lithium aluminum hydride (LAH) (0.50 g, 13 mmol) and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 19:1). The title compound was crystallised by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.75 g (27%); mp 70-75°C. ^{1}H NMR (DMSO-d6) δ 1.17 (q, 3H), 1.23 (t, 3H), 2.18 (d, 3H), 2.47 (m, 2H), 2.84-3.07 (m, 2H), 3.15 (m, 1H), 3.37 (m, 1H), 3.42 (d, 2H), 3.46 (s, 2H), 3.67 (m, 1H), 3.74 (m, 2H), 4.30 (m, 1H), 4.76 (br, 1H), 6.71 (d, 1H), 6.80 (d, 1H), 7.06 (d, 1H), 7.16 (t, 1H), 7.27 (t, 2H), 7.33 (d, 2H), 9.29 (d, 1H) and 10.07 (br, 1H). Anal. ($C_{23}H_{33}NO_3 \cdot HCl$) C, H, N.

The starting compound N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

1.1 Trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid

A solution of triethyl phosphonoacetate (22.4 g, 0.10 mol) in THF (150 mL) was added to sodium hydride (80%, 2.7 g, 0.09 mol) under nitrogen during 15 min. The resulting mixture was refluxed for 15 min whereafter a solution of 2-benzyloxy-5-methyl-benzophenone (15.1 g, 0.05 mol) in THF (50 mL) was added. The reaction mixture was refluxed for 19 h. Water and sodium hydroxide (10 g, 0.25 mol) were added and most of the THF was distilled off. Ethanol was added until a clear solution was obtained and the reflux was continued for a few minutes. Water was added to a total volume of 1 L and the mixture was washed with diethyl ether. Hydrochloric acid was added to the water-phase and a crystalline mass was obtained. The pure trans-isomer was obtained by recrystallisation from ethanol. Yield 10.4 g (60%). ^{1}H NMR (DMSO-d6) δ 2.24 (s, 3H), 4.92 (s, 2H), 6.41 (s, 1H), 6.87 (d, 1H), 6.98 (d, 1H), 7.03 (m, 2H) 7.12 (m, 1H), 7.22 (m, 3H), 7.29 (m, 1H), 7,30 (m, 1H) and 7.33-7.39 (m, 3H).

1.2 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 17 mmol) in THF (20 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (6.9 g, 20 mmol), 2-(2-isopropylaminoethoxy)-ethanol, triethylamine (2.5 g, 25 mmol) and hydroxysuccinimide (2.8 g, 24 mmol) in THF (50 mL). The reaction mixture was stirred for 20 h. The solvent was evaporated and the residue chromatographed on silica (gradient from toluene to ethyl acetate). Yield 5.9 g (62%).

1.3 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

A solution of trans-N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (5.9 g, 12 mmol) in acetic acid (50 mL) was hydrogenatated over Pd/C (10 %, 0.5 g) for 16 h. Filtering and evaporation of solvent left a residue that was chromatographed on silica (ethyl acetate). Yield 2.83 g (61 %).

EXAMPLE 2

N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (0.93 g, 2.5 mmol) in THF (20 mL) was added to LAH (0.22 g, 5.6 mmol) and the mixture was stirred at reflux temperature for 30 min. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (chloroform-methanol 9:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.45 g (46%); mp. 230-232°C. ^{1}H NMR (DMSO-d6) δ 1.27-1.70 (m, 10H), 1.88 (br, 1H), 2.05 (d, 1H), 2.17 (s, 3H), 2.42 (br, 1H), 2.60 (s, 3H), 2.85 (br, 2H), 3.34 (m, 1H), 4.30 (t, 1H), 6.72 (d, 1H), 6.80 (dd, 1H), 7.05 (br, 1H), 7.15 (t, 1H), 7.27 (t, 2H), 7.31 (d, 2H), 9.31 (s, 1H) and 10.53 (br, 1H). Anal. ($C_{24}H_{33}NO \cdot HCl$) C, H, N.

The starting compound N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

2.1 N-Cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g,

20 mmol), cycloheptylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at room temperature. Another portion of cycloheptylamine (1.3 g) was added and the reaction mixture was left stirring for another 1 h. The mixture was filtered and the filtrate evaporated. The residue was dissolved in diethyl ether and washed with hydrochloric acid (1M), water and brine in subsequent order. After evaporation of the solvent, the residue was crystallised from toluene-hexane to give 7.3 g (83%). ^{1}H NMR ($CDCl_3$) δ 1.06 (br, 2H), 1.25-1.74 (m, 10H), 2.30 (s, 3H), 3.83 (m, 1H), 4.95 (s, 2H), 5.50 (d, 1H), 6.49 (s, 1H), 6.90-7.08 (m, 4H), and 7.12-7.44 (m, 9H).

2.2 N-Cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of N-cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.4 g, 10 mmol) and methyliodide (4 g, 30 mmol) in DMF (10 mL) was added to sodiumhydride (80 %, 1.2 g, 40 mmol) at ambient temperature and the mixture was stirred for 60 min. Excess sodium hydride was destroyed by adding methanol, and the reaction mixture was then partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallised from toluene-hexane to yield 4.4 g (97%). ^{1}H NMR ($CDCl_3$) (almost 1:1 mixture of rotameres) δ 1.20-1.80 (m, 12H), 2.30 (m, 3H) 2.61 (s, 1.5H), 2.71 (s, 1.5H), 3.93 (m, 0.5H), 4.46 (m, 0.5H), 4.81 (m, 1H), 6.43 (m, 1H), 6.81 (m, 2H) and 7.08-7.35 (m, 10H).

2.3 N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

A solution of N-cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (3.15 g, 7 mmol) in acetic acid (40 mL) was hydrogenated over Pd/C (10%, 0.2 g) for 72 h. The reaction mixture was filtered and the solvent evaporated. The residue was chromatographed

on silica (toluene-ethyl acetate 9:1). Yield 0.95 g (37%). ^{1}H NMR ($CDCl_3$) δ 1.26-1.98 (m, 12H), 2.02 (s, 3H), 2.12 (s, 3H), 2.28 (m, 1H), 2.52 (m, 1H), 2.71 (m, 1H), 4.36 (dd, 1H), 6.39 (s, 1H), 6.76 (s, 2H), 7.15 (m, 2H) and 7.25 (m, 5H).

EXAMPLE 3

N-Cyclohexyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.0 g, 9 mmol) in THF (90 mL) was added to LAH (0.50 g, 13 mmol) in THF (5 mL) and the mixture was stirred at ambient temperature for 2.5 h. The reaction was quenched and the solvent evaporated. The resulting oil was hydrogenated over Pd/C (10%, 1g) in acetic acid (70 mL) for 20 h. After filtration and evaporation of the solvent, the residue was chromatographed on silica (chloroform:methanol 99:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 1.2 g (36%); mp. 179-183°C. ^{1}H NMR (DMSO-d6) δ 1.05 (m, 1H), 1.21-1.38 (m, 4H), 1.51 (d, 1H), 1.74 (br, 2H), 1.86 (br, 1H), 2.00 (d, 1H), 2.17 and 2.19 (s, 3H), 2.39-2.56 (m, 2H), 2.63 (m, 3H), 2.82 (m, 1H), 2.93 (m, 1H), 3.17 (m, 1H), 4.32 (q, 1H), 6.73 and 6.75 (d, 1H), 6.79 and 6.81 (t, 1H), 7.02 and 7.10 (d, 1H), 7.14-7.18 (m, 1H), 7.25-7.29 (m, 2H), 7.33 (t, 2H), 9.34 (br, 1H) and 10.78 (s, 1H). Anal. ($C_{23}H_{31}NO \cdot HCl$) C, H, N.

The starting compound N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide was prepared as follows:

3.1 N-Cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g,

20 mmol), N-methyl-cyclohexylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 2 h. A second portion of DCC (2.5 g, 13 mmol) and N-methyl-cyclohexylamine (1.5 g, 13 mmol) was added and the reaction mixture was left stirring for 16 h. Diethyl ether and hydrochloric acid (1M) were added and the organic phase was washed with brine. The organic layer was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 5.5 g (63%). ^{1}H NMR (DMSO-d6) (almost 1:1 mixture of rotameres) δ 0.88-1.06 (m, 2H), 1.16-1.39 (m, 5H), 1.55 (t, 2H), 1.67 (br, 1H), 2.21 (s, 1.5H), 2.23 (s, 1.5H) 2.56 (s, 1.5H), 2.67 (s, 1.5H), 3.67 (m, 0.5H), 4.05 (m, 0.5H), 4.82 (s, 1H), 4.85 (s, 1H), 6.57 (s, 0.5H), 6.59 (s, 0.5H), 6.84 (dd, 1H), 6.87 (d, 0.5H), 6.89 (t, 1H), 6.95 (dd, 1H), 6.98 (d, 0.5H), 7.12 (dd, 1H), 7.17 (m, 3H), 7.27 (m, 2H), and 7.32 (m, 3H).

EXAMPLE 4

N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamine hydrochloride

Boran·SMe$_2$-complex in THF (7 mL, 14 mmol) was gently refluxed with a weak stream of nitrogen for 30 minutes. N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide (1.55 g, 4.2 mmol) was added to the refluxing solution and the reflux was continued for 1 h. The reaction mixture was partioned between diethyl ether and sodium hydroxide (1M). The solvent of organic layer was evaporated and the residue was chromatographed on silica (toluene-triethylamine 9:1) to yield the free amine. The hydrochloride salt was obtained by dissolving the amine in diethyl ether with the addition of hydrogen chloride in diethyl ether. The resulting oil produced crystals after some time stirring in diethyl ether. Yield 0.39 g (23%); mp. 143-144°C. ^{1}H NMR (DMSO-d6) δ 1.19 (q, 6H), 1.25 (dd, 6H), 2.53 (m, 1H), 2.70 (m, 1H), 2.87 (m, 2H), 3.59 (m, 2H), 4.38 (t, 1H), 7.24 (t, 1H), 7.35 (t, 2H), 7.39 (d,

2H), 7,45 (t, 1H), 7.68 (t, 1H), 7.74 (t, 2H) and 10.25 (br, 1H). Anal. ($C_{22}H_{28}NF_3 \cdot HCl$) C, H, N.

The starting compound N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide was prepared as follows:

4.1 Diethyl N,N-diisopropylacetamide phosphonate

A mixture of triethylphosphite (23 g, 0.14 mol) and N,N-diisopropyl 2-bromoacetamide (29 g, 0.13 mol) was heated to 110°C for 3 h to yield 35 g (97%). The product was used without purification.

4.2 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide

A solution of diethyl N,N-diisopropylacetamide phosphonate (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 29 mmol) during 30 min, keeping the temperature below 30°C. A solution of 2-trifluoromethyl-benzophenone (5.0 g, 20 mmol) in THF (20 mL) was added and the reaction mixture was heated to 50°C and kept at that temperature for 16 h. A second portion of the phosphorous ylide (15 mmol), prepared as above, was added. After another 24 h at 50°C the mixture was partioned between diethyl ether and water. The etheral layer was evaporated and the residue chromatographed on silica (toluene-ethyl acetate 9:1) yielding 3.0 g (41%) as a mixture of the E- and Z-isomers. Labels a and b refer to the different isomers. ^1H NMR ($CDCl_3$-d) δ 0.80 (d, 6Ha), 1.08 (d, 3Hb), 1.24 (t, 6Hb), 1.31 (d, 3Hb), 1.44 (d, 6Ha), 3.32 (m, 1Ha), 3.34 (m, 1Hb), 4.19 (m, 1Hb), 4.32 (m, 1Ha), 6.04 (s, 1Ha), 6.65 (s, 1Hb) and 7.18-7.75 (m, 9Ha, 9Hb).

4.3 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide

A solution of N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide (2.95 g, 8.1

mmol) in ethanol (50 mL) was hydrogenated over Pd/C (10%, 300 mg) at normal pressure for 24 h. The catalyst was filtered off, the solvent partly evaporated and the product collected after crystallisation. Yield 1.78 g (60%). ^{1}H NMR ($CDCl_3$-d) δ 1.16 (m, 6H), 1.30 (m, 6H), 2.86 (dd, 1H), 3.11 (dd, 1H), 3.41 (m, 1H), 4.03 (m, 1H), 5.12 (m,1H) and 7.10-7.78 (m, 9H).

EXAMPLE 5

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(3-pyridyl)-propanamine dihydrochloride

A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide (2.8 g, 8 mmol) in THF (25 mL) was added to LAH (1.3 g, 32 mmol). The reaction mixture was refluxed for 4 h whereafter the reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 99:1) to give 2.2 g. The product (1.3 g, 4 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to -78°C and boron tribromide (1 g, 8 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature during 1 h. The reaction mixture was washed with sodium hydroxide (1M) and brine and the organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 9:1) to give 0.35 g. The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to produce the dihydrochloride as crystals which soon rearranged to a hard glass. ^{1}H NMR (DMSO-d6) δ 1.22 (dd, 6H), 1.28 (dd, 6H), 2.60 (m,1H), 2.70 (m, 1H), 2.93 (m, 2H), 3.60 (m, 2H), 4.60 (t, 1H), 6.85 (t, 1H), 6.89 (d, 1), 7.11 (t, 1H), 7.38 (d, 1H), 7.96 (dd, 1H), 8.46 (d, 1H), 8.75 (d, 1H), 8.85 (s, 1H), 9.90 (br, 1H) and 10.14 (s, 1H).

The starting compound N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide was prepared as follows:

5.1 2-Methoxyphenyl-3-pyridyl-ketone

A solution of 2-bromoanisole (21 g, 0.11 mol) in diethyl ether (100 mL) was added to magnesium turnings during 45 minutes with heating. After the addition the reflux was continued for 15 min. The Grignard reagent was cooled to 0°C and a solution of 3-cyanopyridine (10 g, 0.10 mol) in diethyl ether (100 mL) was added dropwise. The mixture was refluxed for a few minutes. Hydrochloric acid (20 mL, 0.24 mol, conc.) and 2-propanol (20 mL) were added and the reflux was continued for 30 min. Water and diethyl ether were added and the phases separated. The water-phase was made alkaline (2M NaOH) and was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated to yield 17 g. The crude was chromatographed on silica (toluene-ethyl acetate 19:1) to give 3.75 g (19%). ^1H NMR ($CDCl_3$-d) δ 3.76 (s, 3H), 7.01 (d, 1H), 7.10 (t, 1H), 7.41 (dd, 1H), 7.46 (dd, 1H), 4.53 (m, 1H), 8.12 (d, 1H), 8.75 (s, 1H) and 8.94 (s,

5.2 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide

A solution of of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (9.3 g, 33 mmol) in THF (40 mL) was added dropwise to sodium hydride (80 %, 1.0 g, 33 mmol) during 15 min. The mixture was heated to 40°C for 15 minutes and then cooled to 5°C whereafter a solution of 2-methoxyphenyl-3-pyridyl-ketone (4.5 g, 21 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 16 h. The reaction mixture was partioned between diethyl ether and water and the organic phase was dried ($MgSO_4$) and evaporated to yield 7.1 g of solid material. The product was hydrogenated over Pd/C (10%, 0.2 g) in acetic acid (50 mL) for 48 h. The reaction mixture was filtered and the solvent evaporated. The residue was partioned between diethyl ether and hydrochloric acid (1 M) and the phases were separated. The water-phase was made alkaline (2 M

sodium hydroxide) and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and filtered. Crystallisation began and the mixture was diluted with hexane. Filtration gave 2.9 g (40%). ^1H NMR ($CDCl_3$-d) δ 1.14 (dd, 6H), 1.28 (d, 6H), 3.04 (dd, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.05 (m, 1H), 5.00 (t, 1H), 6.84 (d, 1H), 6.92 (t, 1H), 7.19 (m, 3H), 7.57 (d, 1H), 8.39 (m, 1 H) and 8.55 (d, 1H). 1H).

EXAMPLE 6

N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

A solution of N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide (3.1 g, 9.4 mmol) in THF (20 mL) was added to LAH (1.0 g, 25 mmol) and the reaction mixture was stirred at reflux temperature for 2 h. More LAH (0.5 g), was added and the reflux continued for another 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 3:1) to give 0.4 g of the free amine as a syrup. The amine was dissolved in isopropanol/diethyl ether and hydrogen chloride in diethyl ether was added to give the amine salt. Yield 0.32 g (10 %); mp 152-154 °C. ^1H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.26 (dd, 6H), 2.57 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.36 (t, 1H), 6.69 (dd, 1H), 7.14 (m, 1H), 7.22 (m, 2H), 7.29 (m, 1H), 7.32 (d, 2H), 7.33 (s, 2H), 7.54 (m, 1H) and 10.24 (br, 1H). Anal. ($C_{21}H_{28}NF \cdot HCl$) H, N; C: calcd, 72.1; found, 72.6.

The starting compound N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide was prepared as follows:

6.1 trans-N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide

A solution of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 25

mmol) during 30 min, keeping the temperature below 40°C. A solution of 2-trifluoromethyl-benzophenone (4.0 g, 20 mmol) in THF (10 mL) was added and the reaction mixture was stirred at ambient temperature for 30 min. The mixture was partioned between diethyl ether and brine. The organic layer was dried ($MgSO_4$) and evaporated to give a crystalline mass. Recrystallisation from hexane yielded 3.9 g (60 %). ^1H NMR ($CDCl_3$-d) δ 0.85 (d, 6H), 1.39 (d, 6H), 3.29 (m, 1H), 4.27 (m, 1H), 6.29 (s, 1H), 7.10 (m, 3H) and 7.30 (m, 6H).

6.2 N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide

A solution of trans-N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide (3.25 g, 10 mmol) was hydrogenated over Pd/C (10%, 300 mg) in acetic acid (30 mL) for 24 h. The catalyst was filtered off and the solvent was evaporated to yield 3.15 g (96%). ^1H NMR ($CDCl_3$-d) δ 1.12 (q, 6H), 1.28 (q, 6H), 3.05 (d, 2H), 3.38 (m, 1H), 4.03 (m, 1H), 4.93 (t, 1H) and 6.94-7.32 (m, 9H).

EXAMPLE 7

(R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

Hydrogen chloride in diethyl ether was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine (0.81 g, 2.4 mmol) in diethyl ether and 2-propanol. Crystals were filtered to yield 0.4 g (45%); mp 178-179°C. $[\alpha]_{Hg}$ = -40° (c 1.1 in methanol). ^1H NMR (DMSO-d6) δ 1.16 (d, 3H), 1.20 (d, 3H), 1.24 (d, 3H), 1.27 (d, 3H), 2.54 (m, 2H), 2.84 (m, 1H), 2.97 (m, 1H), 3.58 (br, 2H), 4.38 (t, 1H), 7.08 (d, 1H), 7.22 (t, 1H), 7.32 (m,4H), 7.65 (dd, 1H), 7.83 (d, 1H), 9.80 (s, 1H), 9.86 (br, 1H) 10.99 (s, 1H). Anal. ($C_{22}H_{29}NO_2 \cdot HCl$) H, N; C: calcd, 70.3; found, 70.8.

The starting compound (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine was prepared as follows:

7.1 (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine

DDQ (1.1 eq) was added to a solution of (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine mandelate (prepared as described in WO 94/11337, Example 1) (2.46 g, 5 mmol), dichloromethane (20 mL) and phosphate buffer (pH 7) (0.1 mL). Thereafter, sodium hydroxide solution (20 mL, 1 M) and diethyl ether were added and the phases were separated. The water-phase was extracted twice with dichloromethane-diethyl ether (2:1). The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate-hexane to yield 1.35 g (80 %).

EXAMPLE 8

(R)-N,N-Diisopropyl-3-[5-(7-hydroxy-2-aza-5-oxaheptyl)-2-hydroxyphenyl]-3-phenylpropanamine di-(S)-mandelate

Sodiumcyanoborohydride (0.25 g, 3.9 mmol) was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine (Example 7.1), (1.25 g, 3.7 mmol) and 2-ethoxy-(2-amino)-ethanol (19.5 g, 18 mmol) in methanol (10 mL). Hydrochloric acid (conc) was added to adjust pH to about 3. After 3h, the pH was adjusted to about 1 and the solvent was evaporated. The residue was partioned between diethyl ether and water, whereafter the organic layer was evaporated and the residue chromatographed on silica (chloroform-triethylamine-methanol 88:10:2). The pure amine was dissolved in 2-propanol-diethyl ether with (S)-mandelic acid (2 eq), whereby the product crystallised (the crystals were unstable and an oily mass was soon obtained). Yield 0.2 g (7%); mp dec. ^1H NMR (free amine) ($CDCl_3$-d) δ 1.05 (d, 6H), 1.09 (d, 6H), 2.10 (m, 1H), 2.35 (m, 2H), 2.67 (m, 3H), 3.19 (m, 2H), 3.47 (m, 2H), 3.49 (t, 2H), 3.56 (d, 2H),

3.63 (t, 2H), 4.45 (dd, 1H), 6.75 (d, 1H), 6.79 (d, 1H), 6.95 (dd, 1H), 7.18 (m, 1H) and 7.26-7.33 (m, 4H).

EXAMPLE 9

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine hydrochloride

A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (0.92 g, 2 mmol) in ethanol (30 mL) was hydrogenated over Pd/C (10%, 50 mg) at room temperature for 2 h. The catalyst was filtered off and the solution was treated with hydrogen chloride to obtain the amine salt. Yield 0.66 g (81 %); mp 177-178°C; $[\alpha]_D$ = -23° (c 1.0, methanol). ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.25 (dd, 6H), 2.48 (m, 2H), 2.85 (m, 1H), 2.95 (m, 1H), 3.58 (m, 2H), 3.78 (s, 3H), 4.38 (t, 1H), 6.98 (d, 1H), 7.20 (m, 1H), 7.31 (d, 2H), 7,32 (s, 2H), 7.69 (dd, 1H), 7.81 (d, 1H), 9.85 (br, 1H), 10.74 (s, 1H). Anal. ($C_{23}H_{31}NO_3 \cdot HCl$) H, N, C.

EXAMPLE 10

N,N-Diisopropyl-3-(2-hydroxymethyl)phenyl-3-phenylpropanamine hydrochloride

A solution of N,N-diisopropyl-3-(2-carboxyphenyl)-3-phenylpropanamine hydrochloride (1.88 g, 5 mmol) in THF (30 mL) was added to LAH (1.5 g, 38 mmol) and the reaction mixture was stirred att ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was dissolved in hot diethyl ether-2-propanol (100 mL, 1:4), whereafter HCl in diethyl ether was added. After cooling the product was filtered and dried at 60°C (vacuum). Yield 1.2 g (68%); mp 223-224°C. ^{1}H NMR (DMSO-d6) δ 1.18 (t, 6H), 1.25 (q, 6H), 2.91 (m, 2H), 3.26 (disturbed by solvent, 2H), 3.57 (m, 2H), 4.38 (t, 1H), 4.43 (d, 1H), 4.74 (d, 1H), 5.22 (s, 1H), 7.20 (q, 2H), 7.25-7.35 (m, 5H), 7.40 (dd, 2H), 9.95 (s, 1H). Anal. ($C_{22}H_{31}NO \cdot HCl$) H, N, C.

EXAMPLE 11

(S)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

(S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (0.67 g, 1.5 mmol) was hydrogenated over Pd/C (10%, 67 mg) at atmospheric pressure overnight in ethanol (20 mL). The catalyst was filtered off and the solvent was evaporated. The residue was partioned between diethyl ether and sodium hydroxide (1 M). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The amine salt was obtained by dissolving the amine in diethyl ether-isopropanol and treatment with hydrogen chloride in diethyleter. Yield 0.37 g; mp 219-221 °C; $[\alpha]_D$ -11.4° (c=1.0, methanol); ^1H NMR (CD_3OD) δ 1.30 (d, 12H), 2.36-2.60 (m, 2H), 2.68 (t, 2H), 3.05 (t, 2H), 3.60-3.72 (m, 4H), 4.40 (t, 1H), 6.73 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.17-7.38 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

The starting compound (S)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxy)ethylphenyl]-3-phenylpropanamine was prepared as follows:

11.1 (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

A mixture of (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8 g, 12.7 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), tri-o-tolyl-phosphine (74 mg, 0.14 mmol) and tributylamine (5.9 mL, 24.5 mmol) in dimethylacetamide (50 mL) was heated to 60 °C under nitrogen atmosphere. Ethene (g) was then added to 8 bars pressure. After stirring overnight the reaction mixture was allowed to cool to room temperature. Nitrogen was flushed through the reaction vessel, and toluene and water were added. The aqueous layer