FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **41946/32854**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): New **10/130214**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/11309	**15 NOVEMBER 2000**	**16 NOVEMBER 1999**

TITLE OF INVENTION
STABLE SALTS OF NOVEL DERIVATIVES OF 3,3,-DIPHENYLPROPYLAMINES

APPLICANT(S) FOR DO/EO/US
MEESE, Claus

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☒ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Certificate of Express Mailing;
    Postcard
    Statement Under 37 CFR 3.73(b)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
New 10/130294	PCT/EP00/11309	41946/32854

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	30- 20 =	10	x $18.00	$	180.00
Independent claims	10- 3 =	7	x $80.00	$	560.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	270.00
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
SUBTOTAL =				$	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	40.00
TOTAL FEES ENCLOSED =				$	1910.00
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1910.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-0823. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to review (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Paul A. Lesko, Esq.
Thompson Coburn LLP
One U.S. Bank Plaza
St. Louis, MO 63101
Telephone No.: 314.552.6443
Facsimile No.: 314.552.7000

Signature

Paul A. Lesko
Name

45,364
Registration Number

#4/a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: MEESE, Claus et al.	**Examiner:** To be assigned
Application No.: To be assigned	**Group Art Unit:** To be assigned
Filed: Herewith	
Title: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES	**Docket No.:** 41946/32854

Commissioner for Patents
Box PCT
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the filing fee and examination on the merits, kindly amend the above-identified patent application per the following instructions.

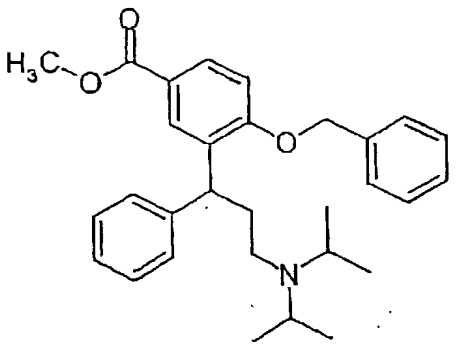
Kindly amend the specification at page one after the title and before the first line of text, by inserting at that point the following sentence -- This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

The amendments to claims 18-21, 23-25, 27, and 28 are pursuant to an Article 34 amendment made to the PCT application on October 5, 2001.

IN THE CLAIMS

At page 56, amend claims 18-21, 23-25, 27, and 28 as follows:

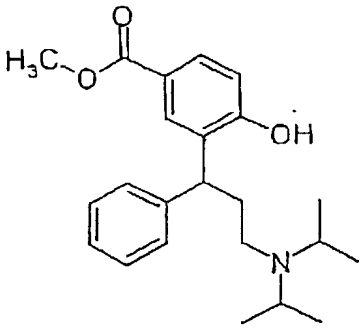
18. (once amended) Compound of formula III



Formula III

in highly pure, crystalline and stable form.

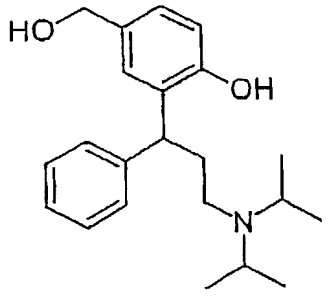
19. (once amended) Compound of formula V



Formula V

in highly pure, crystalline and stable form.

20. (once amended) Compound of formula VI

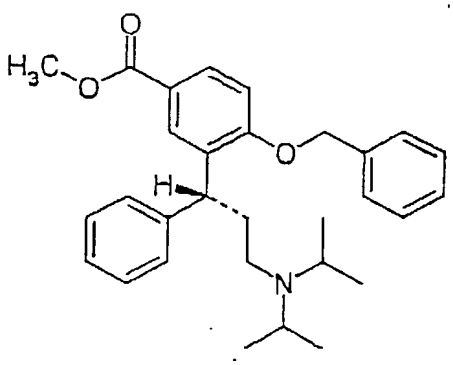


Formula VI

in highly pure, crystalline and stable form.

21. (once amended) Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

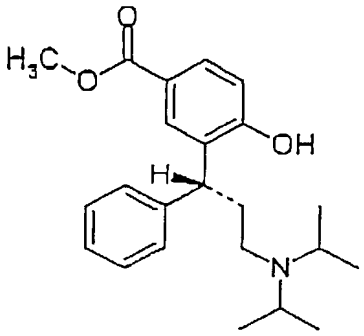
23. (once amended) Compound of formula 3



Formula 3

in highly pure, crystalline and stable form.

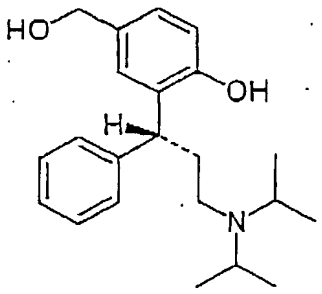
24. (once amended) Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. (once amended) Compound of formula 6

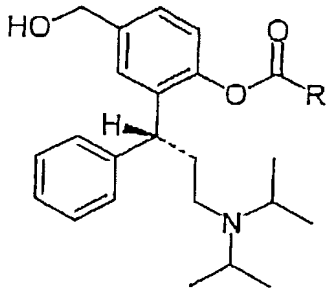


Formula 6

in highly pure, crystalline and stable form.

27. (once amended) Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. (once amended) Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Kindly consider this preliminary amendment and enter it into the record of this application. Attached is a clean copy of the claims. All correspondence should to be directed to Paul A. Lesko, Thompson Coburn LLP, One U.S. Bank Plaza, St. Louis, MO 63101, Telephone No.: 314.552.6443, Facsimile No.: 314.552.7000.

Respectfully submitted,

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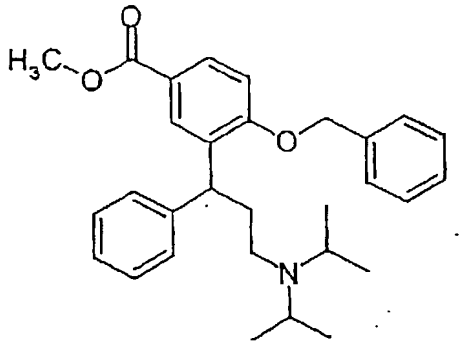
Telephone: 314.552.6443
Facsimile: 314.552.7000

CLEAN COPY OF PARAGRAPH TO BE INSERTED INTO SPECIFICATION

-- This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

Claims

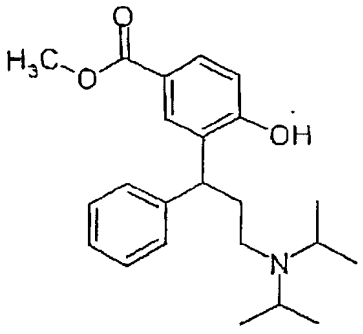
18. Compound of formula III



Formula III

in highly pure, crystalline and stable form.

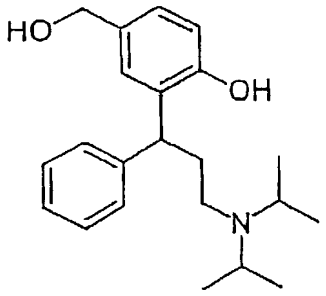
19. Compound of formula V



Formula V

in highly pure, crystalline and stable form.

20. Compound of formula VI

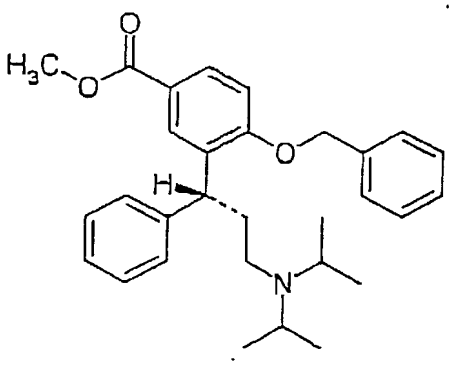


Formula VI

in highly pure, crystalline and stable form.

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

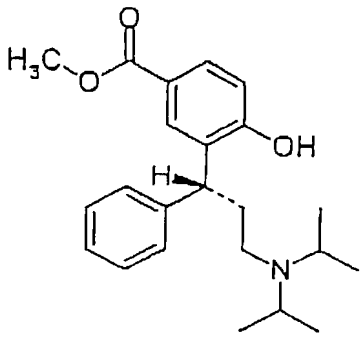
23. Compound of formula 3



Formula 3

in highly pure, crystalline and stable form.

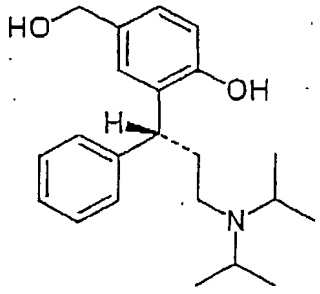
24. Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. Compound of formula 6

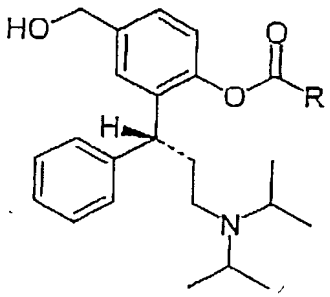


Formula 6

in highly pure, crystalline and stable form.

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



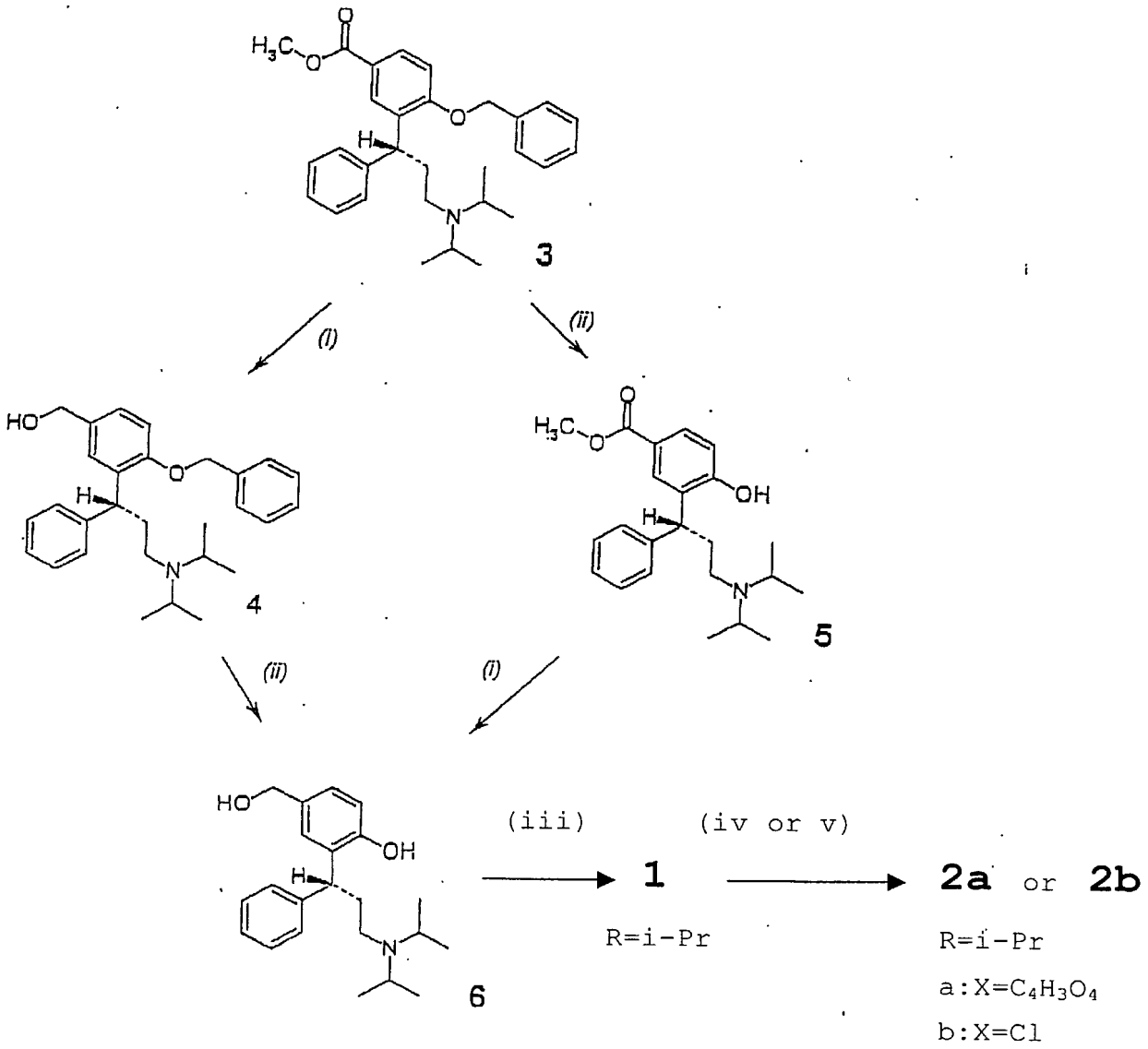
Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



SPECIFICATION

Stable salts of novel derivatives of 3,3-diphenylpropylamines

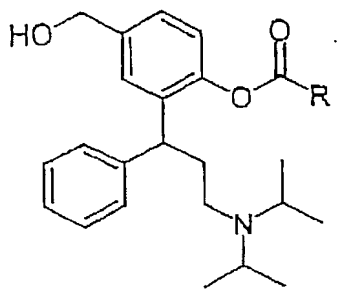
The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugs for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourable metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylamines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below



Formula A

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

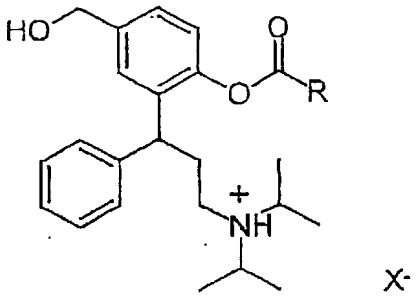
Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification.

During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

Basically salts of the compounds of general formula A can be obtained if solutions of the compounds of formula A (base component) are purified with solutions of acids in suitable solvents, but the salts obtained in the form of solid matter can prove to be altogether amorphous and/or hygroscopic and cannot be directly crystallized from the normal solvents either. Such salts have inadequate chemical stability to be galenically processed as valuable pharmaceutically active substances.

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been prepared under a special reaction process, are converted with a physiologically compatible inorganic or organic acid with general formula H-X, in which ^-X represents the respective

acid residue, into their respective salt with general formula I.



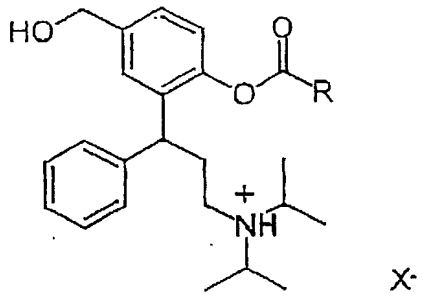
Formula I

The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

A further problem for the present invention is to provide a method for manufacturing such highly pure, crystalline, stable compounds in the form of their salts, as well as highly pure, stable intermediate products.

The final problem for the invention is to provide a method for manufacturing the abovementioned compounds with which a high yield of the products of the process and the respective intermediate products can be obtained chemo- or regioselectively.

This problem is solved in that highly pure, crystalline, stable compounds of the 3,3-diphenylpropylamines in the form of their salts with general formula I are provided,



Formula I

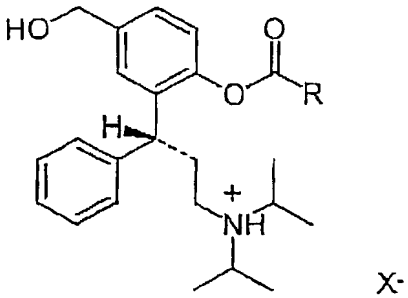
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with a design of the invention the salts of general formula I can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid

(3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

In accordance with a further design form of the invention *R*-configured compounds with general formula 2 are provided



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with an advantageous design form of the invention the compounds in the form of their salts of general formula 2 can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-

glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate

- and

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Furthermore, compounds are preferred in which R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

Particular preference is for [(R)-3-(2-{1-[4-(1-cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenylpropyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-

propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride and {(R)-3-[2-(1-cyclohexyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride.

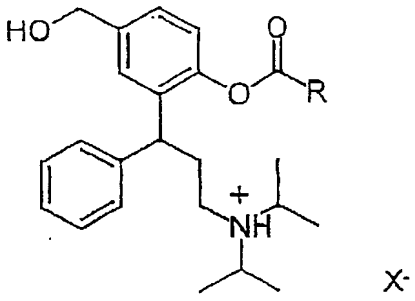
In the compounds of the present invention the expression "alkyl" preferably stands for a straight-chain or branched-chain hydrogen group with between 1 and 6 C-atoms. Special preference is for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The expression "cycloalkyl" designates cyclical hydrogen groups, that have between 3 and 10 hydrogen atoms, that may also contain suitable substitutes in place of the hydrogen atoms.

The expression "phenyl" designates a $-C_6H_5$-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable halogens are fluorine, chlorine, bromine and iodine atoms

The present invention also includes methods for manufacturing the compounds in accordance with the invention of general formula I as well as valuable intermediate products.

The method is characterised by chemo- and regioselectivity.

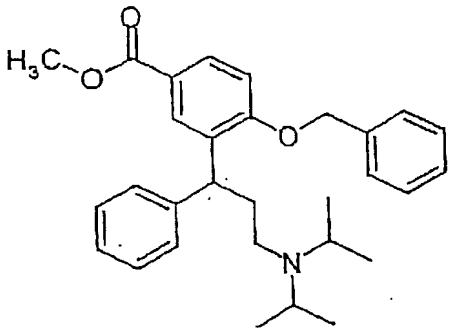
Compounds of general formula I



Formula I

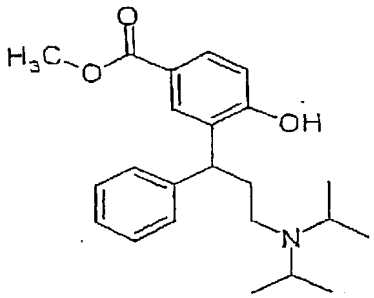
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are manufactured in that

a) a compound of formula III



Formula III

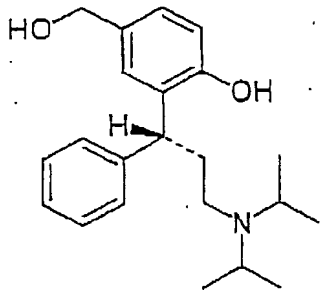
is split with a hydrogenation agent to form a compound of formula V



Formula V

whereupon

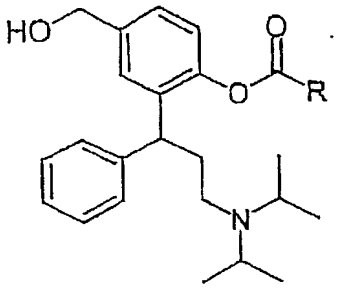
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

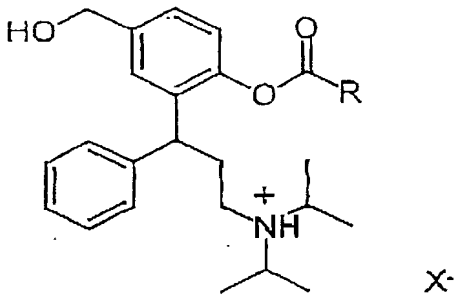
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

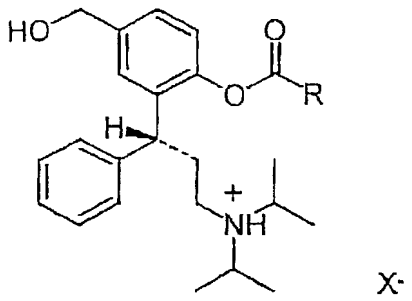


Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with the invention, for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

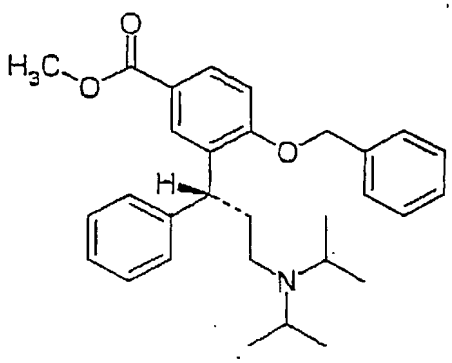
In accordance with an advantageous further development of the invention a method for the manufacture of *R*-configured compounds of the general formula 2 is described,



Formula 2

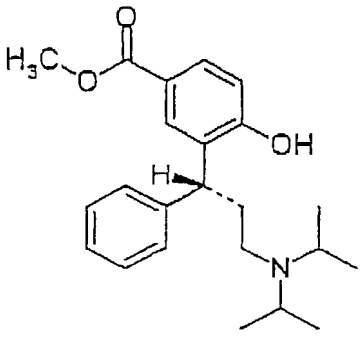
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, in that

a) a compound of formula 3



Formula 3

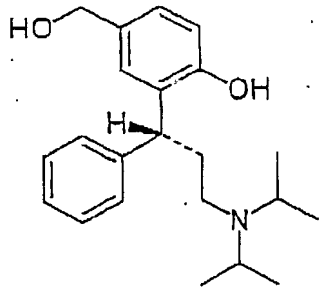
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

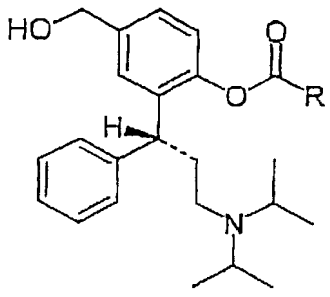
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

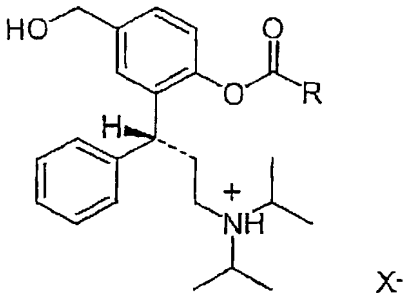
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

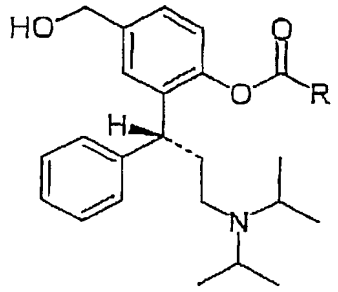
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

Advantageously in order to obtain compounds of general formula 2, in accordance with the method hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Particular advantageously, on the basis of the crystalline *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)benzoic acid methyl ester, the highly pure,

crystalline intermediate product *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester is prepared, which is reduced to *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, is finally acylated in a suitable manner and is then converted with a physiologically compatible inorganic or organic acid under spontaneous crystallisation to the respective highly pure, crystalline, stable salt.

Depending on the acid chloride used, compounds of general formula 1 are obtained,



Formula 1

in which R denotes C_1-C_6-alkyl, in particular isopropyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

In order to obtain the compounds in accordance with the invention in the form of their salts the special reaction process via particular intermediate stages and individually identifiable intermediate products is crucial.

This is explained using reaction diagram 1 (see Figure 1), in which the conversions with *R*-configured compounds are described, but without this being restrictive.

In this:

3 = ***R***-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid- methyl ester

4 = ***R***-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5 = ***R***-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

6 = ***R***-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1 = ***R***-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester

2a = ***R***-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl-isobutyrate ester hydrogen fumarate

2b = ***R***-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydro xymethylphenyl-isobutyrate ester hydrochloride hydrate

In accordance with the reaction process explained in the embodiment the preliminary stage 3 (*R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methylester) is prepared in crystalline, pure form.

Using normal methods - such as BBr_3, $AlCl_3$ - but preferably by means of hydrogen gas via Raney nickel in methanol as the solvent at room temperature (RT), preliminary stage 3 is split into 5 (*R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methylester. This develops in highly pure, crystalline form (melting point 143.7 °C).

Finally, using a suitable reducing agent - such as $NaBH_4$/EtOH - preferably $LiAlH_4$ 5 is reduced into an inert solvent at low

temperature (-78°C to + 10°C) and the compound 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) is obtained. The compound 6 is obtained in a highly pure state and can be crystallised from a suitable solvent such as ethyl acetate. The colourless, compact grained material has a melting point of 102.3°C. This is surprising in that the compound 6 in the state of the art is described as an amorphous solid.

Compound 6 is now acylated with very good yield and regio- and chemoselectivity, into a phenolic ester. This reaction is performed at RT or low temperatures with an equivalent acid chloride in the presence of a base in a suitable solvent. Suitable solvents are ethyl acetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene.

The reaction is preferably performed with isobutyrylchloride as the acid chloride and triethylamine as the base at the abovementioned temperatures. The 1 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester) then obtained, occurs with such purity that with solutions of the fumaric acid in suitable solvents spontaneous crystallisation starts with the formation of the hydrogen fumarate salt 2a.

This salt has a high melting point of 103°C, is stable at RT, is non-hygroscopic and does not contain crystallose agents. It can be recrystallised as often as desired.

If instead of fumaric acid anhydrous hydrochloric acid is used - for example as an etheric solution - salt formation also takes place with the crystalline product 2b (*R*-(+)-2-(3-

diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate being obtained.

Following a further recrystallisation the product 2b has a melting point range of 97 - 106°C.

Finally the product 2b can particularly advantageously be obtained by the following variants of the inverse reaction process, starting with the compound 6 of reaction diagram 1. The product 2b can thus be obtained without the addition of an external acid-intercepting base, as explained in the following.

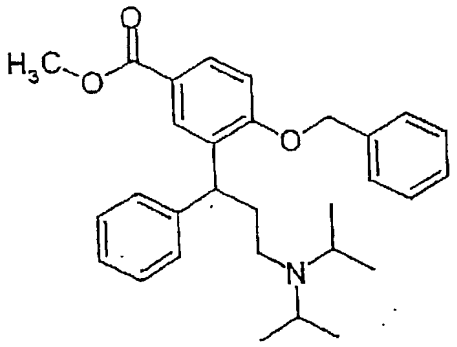
Solutions of 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) are dripped into solutions of isobutyrate chloride, so that under suitable polarity conditions the anhydrous product 2b rapidly crystallises out. 2b is very hygroscopic.

If the abovementioned reaction is carried out in a humid solvent, that contains at least one mole equivalent of water, a stable and crystalline, hydrate-containing product 2b is obtained, that has the abovementioned melting characteristics.

The compounds in accordance with the invention of general formulae 1 and 2 are suited to bulk material.

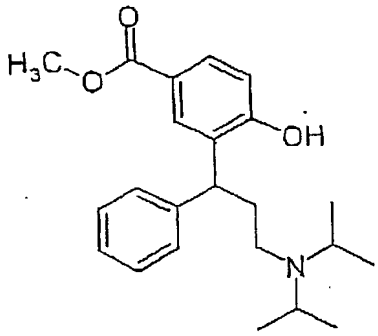
Of particular advantage are the highly pure compounds of general formulas III, V, VI, 3, 5, 6 and 7 which can be obtained.

Compound of formula III



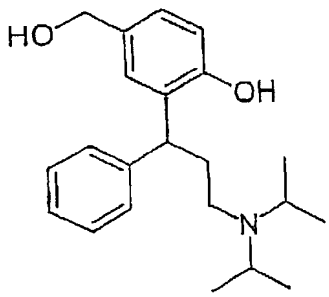
Formula III

Compound of formula V



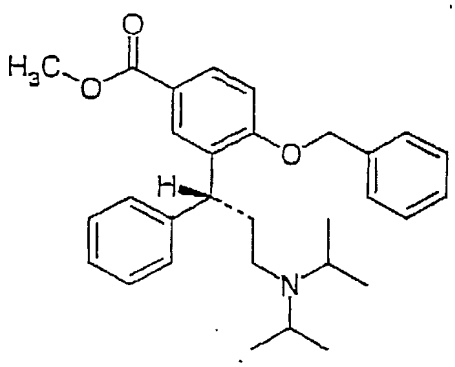
Formula V

Compound of formula VI



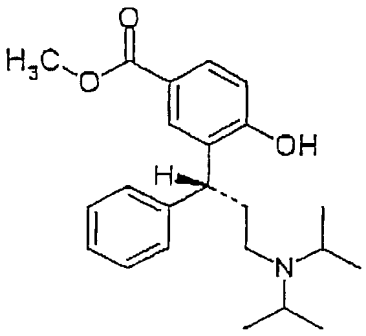
Formula VI

Compound of formula 3



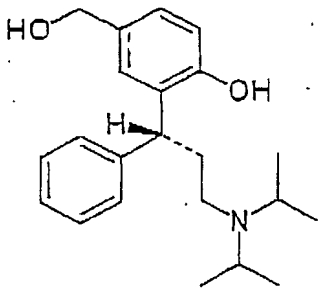
Formula 3

Compound of formula 5



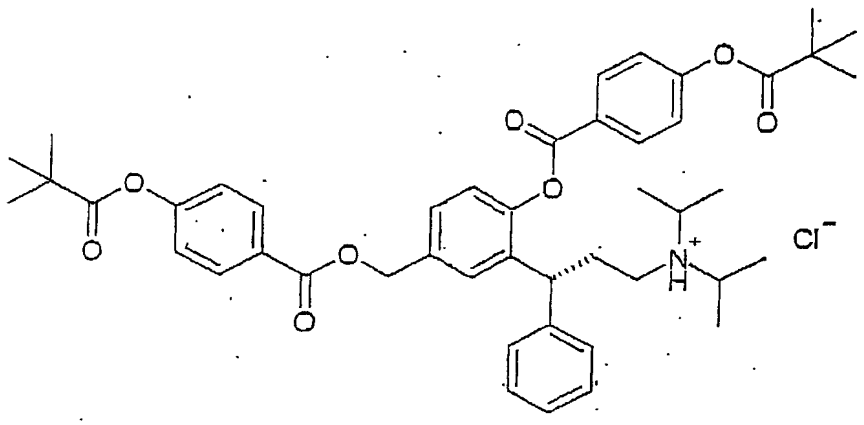
Formula 5

Compound of formula 6



Formula 6

Compound of formula 7



Formula 7

[(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chloride

The abovementioned compounds III, V, VI, 3, 5, 6 and 7 are particularly suited to use in each case as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

Of particular advantage are compounds for use as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Finally, the method can be carried out in a particularly advantageous way by converting a compound of general formula 6 (see reaction diagram 1) with an equivalent isobutyryl

chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester.

In accordance with the invention *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is particularly suited to conversion with fumaric acid or hydrochloric acid with the formation of the respective salt.

The following embodiments explain the invention.

Experimental

I. General

All compounds have been fully characterised by ^{1}H and ^{13}C NMR-spectroscopy (Bruker DPX 200). The stated chemical displacements in the ^{13}C-NMR-spectra (50 MHz, ppm values stated) refer to the solvent resonances of $CDCl_3$ (77.10 ppm). ^{1}H NMR data ($CDCl_3$; 200 MHz, ppm) refer to internal tetramethylsilane).

Thin layer chromatography (DC, R_f given) was carried out on 5x10 cm E. Merck silica gel films (60F254), and the stains were revealed by fluorescence erasure or by spraying with alkaline potassium permanganate solution.

Absorbent systems were: (1), n-hexane / acetone / triethylamine (70/20/10, v/v-%); (2), toluene / acetone / methanol / acetic acid (70/5/20/5, v/v-%).

The optical rotations were measured at a wavelength of 589.3 nm (sodium D-line), at room temperature using ethanol as a solvent (apparatus: Perkin Elmer Polarimeter Type 241), melting points (in °C) are uncorrected and were determined on the Mettler FP apparatus, or by differential thermoanalysis (DSC) on the Perkin Elmer Model DSC7, using "Pyris" evaluation software.

UV/VIS measurements were carried out on the spectrophotometer model Lambda 7 (Perkin-Elmer) with a layer thickness of 1 cm. The specific absorption stated is for a 1% solution ($A^{1\%}_{1\ cm}$).

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer Series 1610 (resolution 4 cm^{-1}).

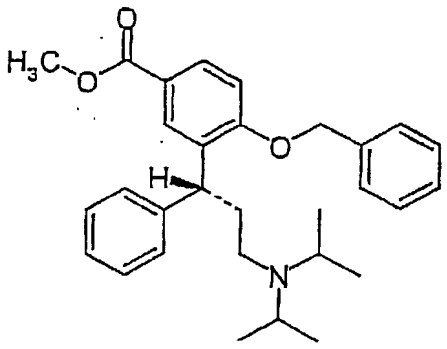
Gas chromatography mass spectrometry (GC-MS, m/z values and relative intensity with reference to the base ion (%)) was carried out with a Finnigan TSQ 700 Triple Mass Spectrometer in positive (P-CI) or negative (N-CI) chemical ionisation measurement mode with methane or ammonium as a reactant gas or via electron impact ionisation. Hydroxy compounds were measured as trimethylsilylether-derivatives.

Coupled liquid chromatography-mass spectrometry (LC-MS): Waters Integrity System, Thermabeam Mass Detector (EI, 70 eV), m/z-values and relative intensity (%) are given over a quantity range of 50-500 a.m.u.

II. Embodiments

The Arabic numerals in brackets (3), (4), (5), (6) refer to the identical designations in reaction diagram 1.

1. Preparation of
R-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methylester (3)



A solution of *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid hydrochloride (2.30 kg, 4.77 Mol) in 26.4 litres of methanol and 0.25 litre of concentrated sulphuric acid is heated for 16 hours with recycling. Then a third of the solvent is distilled off, cooled and under agitation mixed with 5 kg ice and 2.5 litres 25% aqueous sodium carbonate solution. The deposit is first extracted with 15 litres and then again with 5 litres of dichloromethane. The organic phases are purified and concentrated on the rotary evaporator until dry. 1.99 kg (90.7% of theoretical) dark yellow oil with a purity of approximately 90% (DC, NMR) are obtained.
DC (1): 0.58

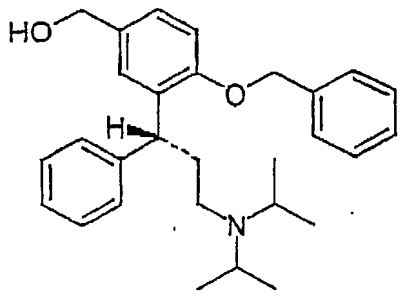
^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.83, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22,129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Recrystallisation

69.0 oily raw material is dissolved in 150 ml boiling methanol. Following the addition of 15 ml distilled water it is left at 0°C, whereupon colourless crystals precipitate. These are filtered off, washed with a little cold methanol and vacuum-dried. Yield: 41.8 g (60.6 % of theoretical) colourless crystals, melting point 89.8 °C; $[I]_D^{20}$ = - 30.7 (c = 1.0, ethanol).

2. Preparation of

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)



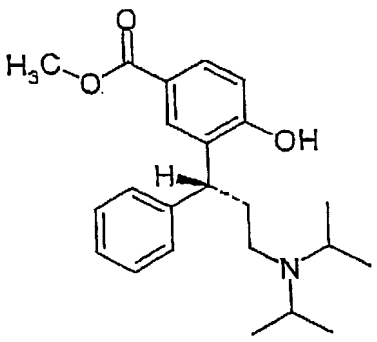
Raw product (3) (28 g) is dissolved in 230 ml pure diethylether and under agitation is dripped into a suspension of 1.8 g lithium-aluminium hydride in diethylether (140 ml). After 18 hours of agitation at room temperature, 4.7 ml of water are added in drop form. The organic phase is separated

off, dried with anhydrous sodium sulphate, filtered and concentrated on the rotary evaporator until dry. 26 g (98.9% of theoretical) *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) are obtained as a colourless oil.

DC (2): 0.32; $[I]_D^{20}$ = + 6.3 (c = 1.0, ethanol).

^{13}C-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.

3. Preparation of *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5)



To an agitated suspension of 5g Raney nickel (washed with water, then with methanol) in 200 ml methanol, 10 g (21.8 mmol) *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl ester (3) are added. Following brief heating, in order to dissolve all (3) completely, the apparatus is placed under a hydrogen gas atmosphere. After three hours of agitation at normal pressure and room temperature, the thin layer chromatography demonstrates

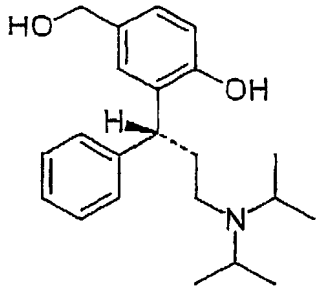
complete conversion. The deposit is rinsed with nitrogen gas and following addition of some active charcoal is filtered. Following concentration of the methanolic solution on the rotary evaporator 6.0 g (75% of theoretical) *R*-(-)-3-(3-diisopropylaminophenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5) remains in the form of colourless crystals with a purity of 99.6 % (HPLC).

Melting point 143.7 °C; DSC 144.7°C

$[I]_D^{20}$ = -26.6 (c = 0.93, ethanol).

^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Starting from the intermediate stage (4), *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) are dissolved in 220 ml methanol and Raney nickel (5 g). The apparatus is rinsed with hydrogen gas and the deposit is agitated for two days at room

temperature. Following the addition of a further 5 g Raney nickel, agitation for a further two days at room temperature takes place under a hydrogen gas atmosphere, followed by filtration off from the catalyser and concentration until dry on the rotary evaporator. The oily, pale yellow residue is dissolved in 100 ml diethylether, washed twice with 100 ml water each time, dried via sodium sulphate, filtered and concentrated until dry. 14.1 g (90.4% of theoretical) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol are obtained in the form of a cream-coloured, amorphous solid. For recrystallisation see under c).

b) Starting from the intermediate stage (5); *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

A solution of 370 mg (1.0 mmol) *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester in 20 ml anhydrous tetrahydrofurane is slowly and at room temperature dropped into an agitated mixture of dried tetrahydrofurane (10 ml) and a 1M solution of lithium-aluminium hydride in tetrahydrofurane (3 ml) (under a nitrogen protective gas atmosphere). Excess hydride is decomposed by the dropped addition of a saturated sodium carbonate solution. Following separation of the organic phase this is concentrated on the rotary evaporator and then dried in the high-vacuum. 274 mg (74% of theoretical) pale yellow oil is obtained, that slowly solidifies into an amorphous mass.

c) Recrystallisation:

Raw product 6 (1.0 g) is dissolved in ethyl acetate and again concentrated on the rotary evaporator. The diol released in

this way from foreign solvents (diethyl ether or tetrahydrofurane, see above) has 1.5 ml ethyl acetate added with slight heating. Agitation takes place until a clear solution results, followed by cooling at room temperature and addition of a few seed crystals. These are obtained by purifying raw 6 via HPLC, collecting the main fraction, concentrating this and drying the residue for a number of hours in the high-vacuum. Once clear crystallisation has definitely started, it is left at - 10°C. The crystals are sucked off in the cold and dried in the vacuum. Colourless crystals with a yield of 84% are obtained.

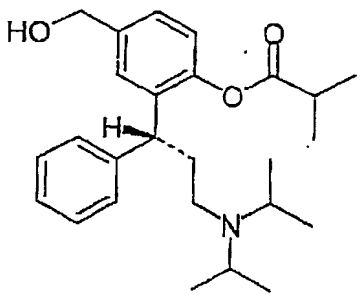
Melting point 102.3 °C

DC (1): 0.57

$[I]_D^{20}$ = +21.3 (c = 1.0, ethanol).

^{13}C-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.

5. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenolisobutyrate ester (1)

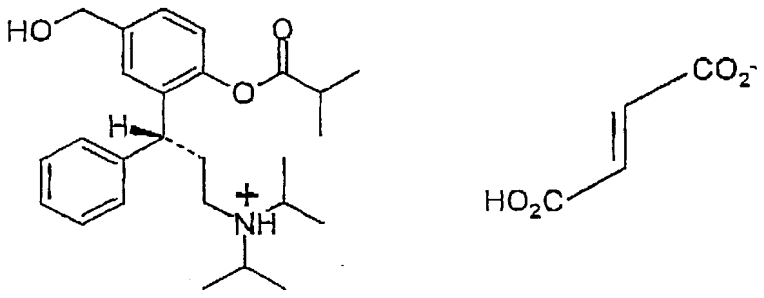


A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) and triethylamine (20.4 g, 201.7 mmol) in 750 ml dichloromethane has a solution of isobutyrate chloride (23.4 g, 201.7 mmol) in 250 ml dichloromethane added under agitation and cooling. Following addition agitation takes place for a further 15 minutes at 0°C, then for 30 minutes at room temperature and then one after another washing with water (250 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic phase is separated and concentrated on the rotary evaporator until dry. The ester *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is obtained as a colourless, viscous oil; yield: 77.1 g (98.4 % of theoretical).

DC (1): 0.26; $[I]_D^{22}$ = + 2.7 (c = 1.0, ethanol).

^{13}C-NMR ($CDCl_3$):19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125.59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.



A solution of 41.87 g (102 mmol) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester in 90 ml 2-butanone has fumaric acid (11.81 g, 102 mmol) added while heating. Following dissolution of the acid, cyclohexane (20-30 ml) is slowly added under agitation until the onset of turbidity. The colourless, homogenous deposit is initially left for 18 hours at room temperature, and then for several hours at 0°C. The colourless crystals that have precipitated are sucked off, washed with a little cyclohexane/2-butanone (90:10, vol.-%)and dried in the vacuum at 30°C. 44.6 g (83.1 % of theoretical) hydrogen furate salt of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester in the form of colourless flakes are obtained.

Melting point 98.8°C, a second crystallisation from the same solvent mixture provides a product with a melting point of 103°C.

$[I]_D^{20}$ = +6.0 (c = 1.0, ethanol).

Elementary analysis: Calculated for $C_{30}H_{41}NO_7$ (molecular weight 527.66) C 68.29 %, H 7.83 %, N 2.65 %, O 21.2 %; found C 68.29 %, H 7.90 %, N 2.72 %, O 21.0 %.

UV/VIS at Σ in nm ($A^{1\%}_{1\ cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

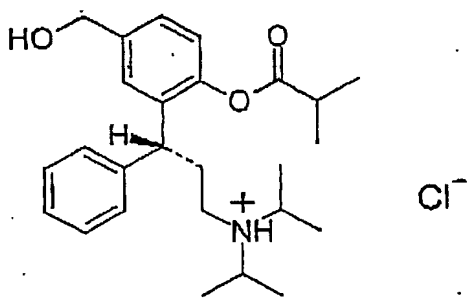
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 ($\underline{C}H_2OH$); 6.832 (=CH, fumarate); 6.84-7.62 (aryl, = CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CH\underline{C}H_2$); 34.09 ($\underline{C}H$-C=O); 41.87 ($CH\underline{C}H_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, fumarate); 170.48 (C=O, fumarate); 175.62 (i-Pr-C=O).

MS in the direct inlet, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrochloride hydrate



A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester (8.54 g, 25.0 mmol) in 50 ml dichloromethane is slowly dropped at 0°C into an agitated solution of isobutyrate chloride (2.66 g, 25.0 mmol) in 100 ml dichloromethane. After an hour the cooling is

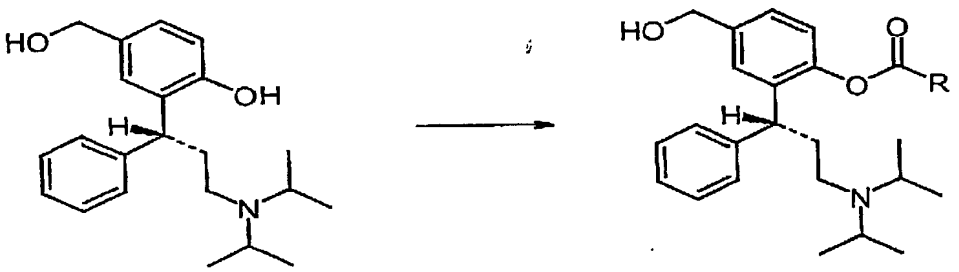
removed and re-agitation takes place for an additional hour. Following the drawing off of the volatile components in the vacuum on the rotary evaporator a colourless, amorphous-solid foam remains. This residue is dissolved in acetone (17 ml), with 0.45 to 0.50 g water and diethyl ether is added (approx. 20 - 25 ml) until there is a definite onset of turbidity. Following brief treatment with ultrasound crystallisation starts spontaneously and under agitation a further 80 ml of diethyl ether are slowly added. The precipitated colourless crystals are sucked off and dried overnight in the vacuum via phosphorous pentoxide. 10.5 g (93.7 % of theoretical) colourless crystalline *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate with a purity of 97.0% (HPLC) are obtained.

Melting point 97.1 °C.

$[I]_D^{20}$ = + 4.3 (c = 1.03, ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolic monoester



General work specification for the manufacture of phenolic monoesters

Into a solution of 120.3 mg (0.352 mmol) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (0.352 mmol) in 2 ml dichloromethane is dropped. Then triethylamine-dichloromethane (49.1µl/0.353 mmol-2 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with 5 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = $CH_2CH(CH_3)_2$

R-(+)-3-methylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester

Colourless oil with 70% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.
DC (1): 0.76.

R = $CH_2C(CH_3)_3$

R-(+)-3.3-dimethylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base

Colourless oil with 69.7% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.
DC (1): 0.75.

R = $(CH_3)_3C$

R-(+)-3-pivalic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless crystals, melting point 165-6 °C.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R = c-C_3H_5

R-(+)-cyclopropane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35, 129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R = c-C_4H_7

R-(+)-cyclobutane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R = c-C_5H_9

R-(+)-cyclopentane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R = c-C_6H_{11}

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm):
174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R = 4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-ethylcarbonyloxy-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless crystals, melting point 195-8 °C.
^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.0 Hz, 1H, Phenyl-H3), 7.41-7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.6 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.97-2.74 (m, 2H, CH_2), 2.67 (q, J = 7.4 Hz, 2H, CH_2), 2.56-2.43 (m, 2H, CH_2), 1.23-1.13 (m, 15H, 2 × CH(C<u>H</u>$_3)_2$, CH_3).

R = 4-(i-$C_3H_7CO_2$)-C_6H_4

R-(+)-4-(isopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 202-4 °C.
^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.4 Hz, 1H, Phenyl-H3), 7.42-7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.99-2.78 (m, 3H, CH_2, C<u>H</u>$(CH_3)_2$), 2.54-2.47 (m, 2H, CH_2), 1.29-1.13 (m, 18H, 3 × CH(C<u>H</u>$_3)_2$).

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-(+)-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base.

Colourless oil.
^{1}H-NMR (DMSO-d_6): 8.19-8.12 (m, 2H, phenyl-H), 7.45-7.33 (m, 3H, phenyl-H), 7.25-7.09 (m, 7H, phenyl-H), 5.20 (t, J = 5.6 Hz, 1H, OH), 4.50 (d, J = 5.6 Hz, 2H, CH_2), 4.20 (t, J = 7.5 Hz, 1H, CH), 2.95-2.80 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.38-2.25 (m, 2H, CH_2), 2.09-2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82-0.76 (m, 12H, 2 × CH(C<u>H</u>$_3)_2$).

Hydrochloride: colourless crystals, melting point 165-6 °C.
^{1}H-NMR ($CDCl_3$): 8.22-8.16 (m, 2H, phenyl-H), 8.02 (d, J = 1.8 Hz, 1H, phenyl-H), 7.27-7.02 (m, 9H, phenyl-H), 4.83-4.60

('m', 2H, CH_2), 4.01-3.94 (m, 1H, CH), 3.66-3.54 (m, 2H), 3.18-2.80 (m, 3H), 2.53-2.44 (m, 1H) (2 × CH_2, 2 × $C\underline{H}(CH_3)_2$), 1.43-1.25 (m, 21H, $(CH_3)_3$, 2 × $CH(C\underline{H_3})_2$).

R = 4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(cyclopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 208-213 °C.
^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H can be substituted with D_2O, NH), 8.15-8.09 (m, 2H, phenyl-H), 7.53 ('d', 1H, phenyl-H3), 7.42-7.13 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.53 (m, 2H, 2 × CH(CH3)2), 3.05-2.70 (m, 2H, CH2), 2.51-2.37 (m, 2H, CH2), 2.01-1.89 (m, 1H, cyclopropyl-CH), 1.20-1.05 (m, 16H, 2 × CH(CH3)2, 2 × cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R = 4-(c-$C_4H_7CO_2$)-C_6H_4

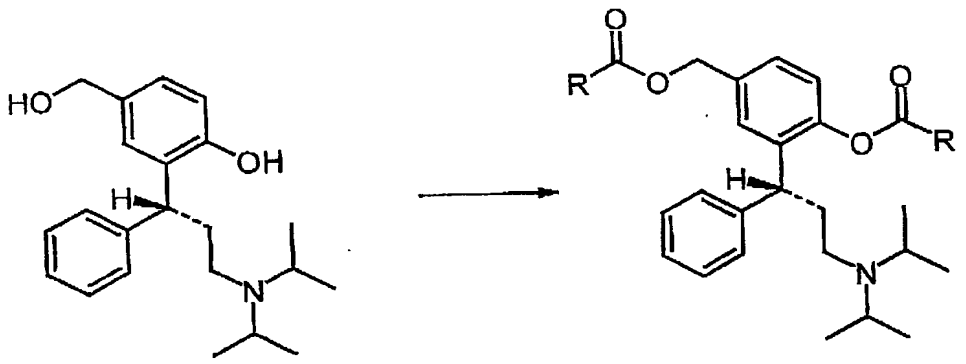
R-(+)-4-(cyclobutylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 201-6 °C.
^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H can be substituted with D_2O, NH), 8.17-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.42-7.14 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.47 (m, 3H, cyclobutyl-CH), 2 × $C\underline{H}(CH_3)_2$), 3.00-2.70 (m, 2H, CH_2), 2.51-2.26 (m, 6H, CH_2, 2 × cyclobutyl-CH_2), 2.10-1.85 (m, 2H, cyclobutyl-CH_2), 1.22-1.12 (m, 12H, 2 × $CH(C\underline{H}_3)_2$).

R = 4-(c-$C_6H_{11}CO_2$)-C_6H_4
R-(+)-4-(cyclohexylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 212-217 °C.
^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, *can be substituted with D_2O*, NH), 8.16-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.39-7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, *can be substituted with D_2O*, OH), 4.53 (d, J = 4.2 Hz, 2H, CH_2), 4.22 (t, J = 7.5 Hz, 1H, CH), 3.62-3.48 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 3.00-2.60 (m, 3H, cyclohexyl-CH), CH_2), 2.51-2.40 (m, 2H, CH_2), 2.07-1.98 (m, 2H, cyclohexyl-CH_2), 1.80-1.11 (m, 20H, 4 × cyclohexyl-CH_2), 2 × $CH(C\underline{H}_3)_2$)

9. **Identical diesters**



General work specification for the manufacture of identical diesters

Into a solution of 7.30 g (21.4 mmol)R-(+)-2-(3-diiso-propylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (49.2 mmol) in 50 ml dichloromethane is dropped. Then triethylamine-dichloromethane (6.86 ml/ 49.2 mmol-50 ml)is added. After 1-3 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 100 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = Methyl

R-(-)-acetic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, free base

Pale yellow oil, purity (HPLC): 95.2%.
^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.
LC-MS: 425 (15%, $M^{+\cdot}$), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).
$[\alpha]_D^{20}$ = -33.1 (c = 1, CH_3CN).
DC (1): 0.79.

R = Cyclohexyl

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Pale yellow oil, purity (NMR): >95%.
^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.
DC (1): 0.96.

R = Isopropyl

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Free base: pale yellow oil, purity (HPLC): 95.6%.
^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.
DC (1): 0.74.

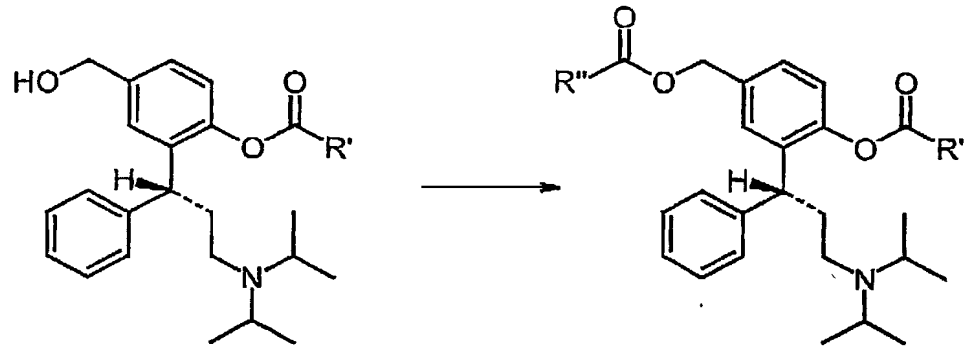
Hydrogen fumarate salt: colourless syrup, 94.4% HPLC purity.
^{13}C-NMR ($CDCl_3$): 17.89,
18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoic acid)-phenyl-ester hydrochloride

Colourless crystals, melting point 105-7 °C.
^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Mixed diesters



R` is not equal to R``

General work specification for the manufacture of mixed diesters

Into a solution of 5.30 mmol phenolic monoester of general formula A in 40 ml dichloromethane under agitation at 0°C a solution of acid chloride (5.83 mmol) in 15 ml dichloromethane is dropped. Then triethylamine-dichloromethane (0.589g/ 5.82 mmol-15 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 50 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following example is manufactured using this method:

R' = $CH(CH_3)_2$

R'' = CH_3

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Colourless oil.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

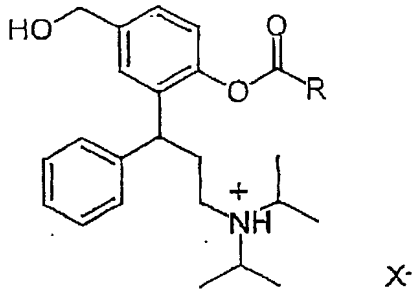
Hydrochloride: colourless crystals

^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$ = +14.6 (c = 1, $CHCl_3$).

CLAIMS

1. Compounds of general formula I



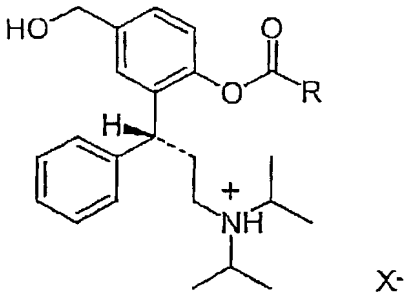
Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

2. Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid,

hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

3. Compounds in accordance with claims 1 and 2, characterised in that they have general formula 2.



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

4 Compounds in accordance with claim 3, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-

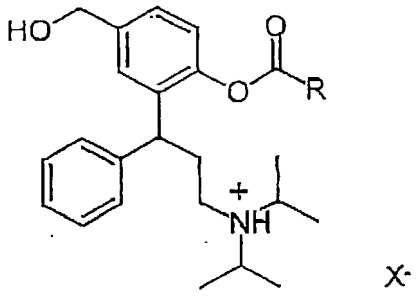
tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

5. Compounds in accordance with claims 3 and 4, characterised in that they are *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate, *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate

6. Compounds in accordance with claims 3 and 4, characterised in that R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

7. Compounds in accordance with claims 1 to 6 in the form of a bulk material.

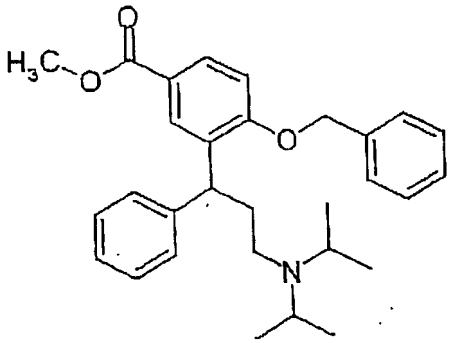
8. Method for manufacturing compounds of general formula I



Formula I

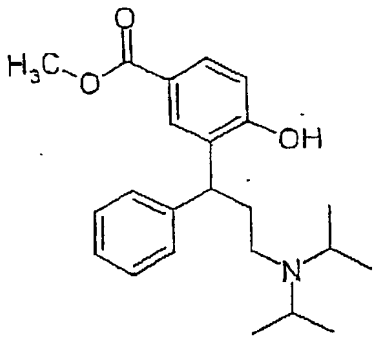
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of formula III



Formula III

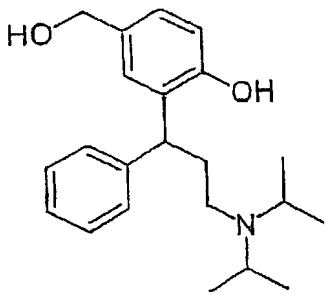
is split with a hydrogenation agent to form a compound of Formula V



Formula V

whereupon

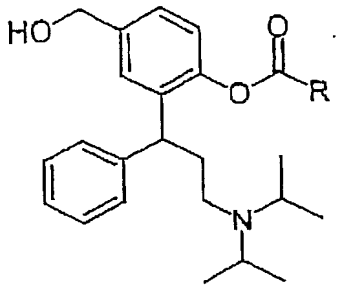
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

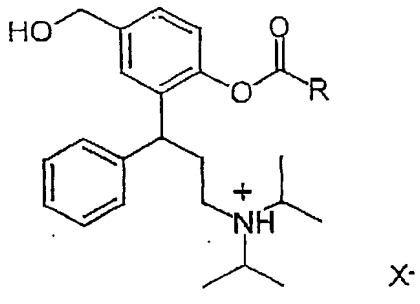
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

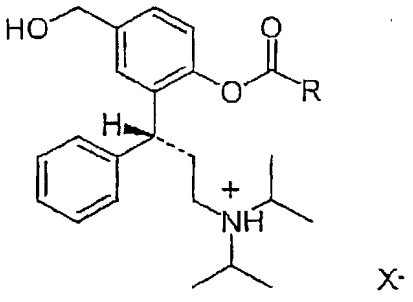


Formula I

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

9. Method in accordance with claim 8, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

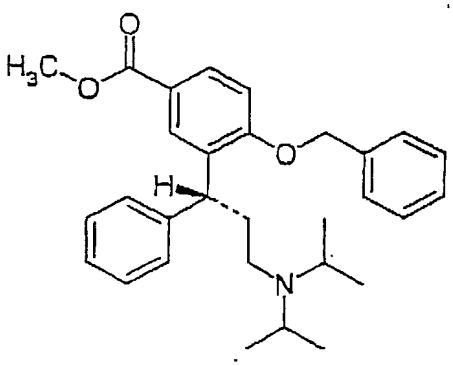
10. Method for manufacturing compounds of general formula 2



Formula 2

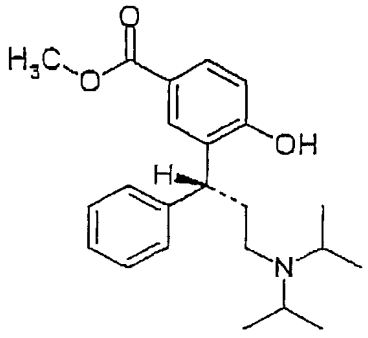
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of the formula 3



Formula 3

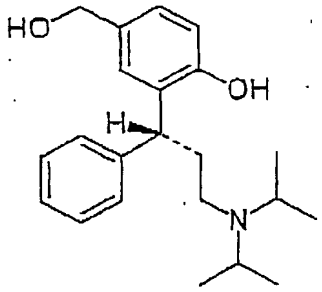
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

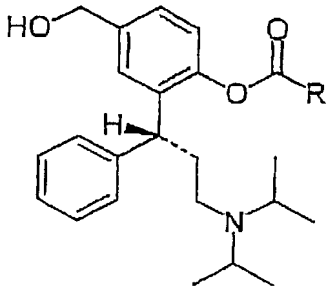
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

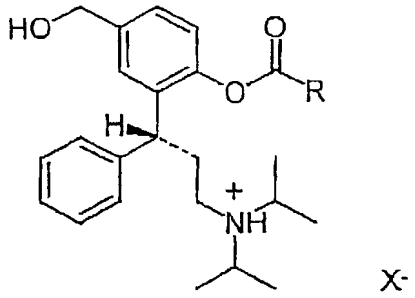
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

11. Method in accordance with claim 10, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-

hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

12. Method in accordance with claims 8 to 11, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

13. Method in accordance with claims 8 to 11, characterised in that for the reducing agent $NaBH_4$/EtOH, preferably $LiAlH_4$/THF, is used.

14. Method in accordance with claims 8 to 11, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

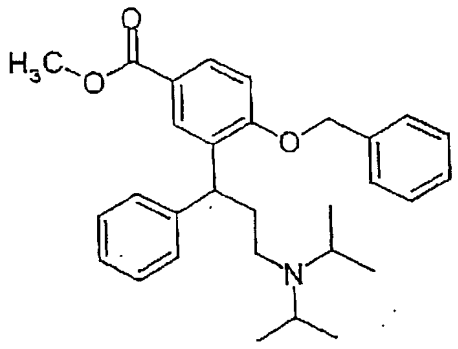
15. Method in accordance with claims 10 to 14, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate.

16. Method in accordance with claims 10 to 15, characterised in that *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid or

hydrochloric acid are converted with the formation of the respective salt.

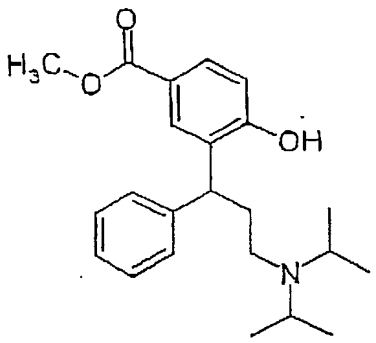
17. Method in accordance with claims 10 to 13 for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of isobutyrate chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

18. Compound of formula III



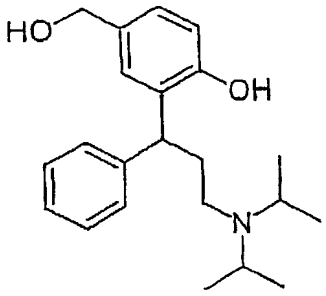
Formula III

19. Compound of formula V



Formula V

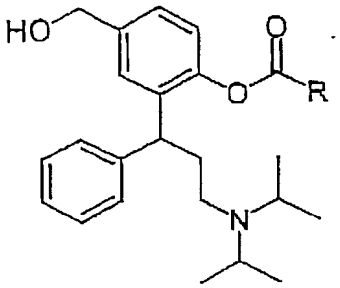
20. Compound of formula VI



Formula VI

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

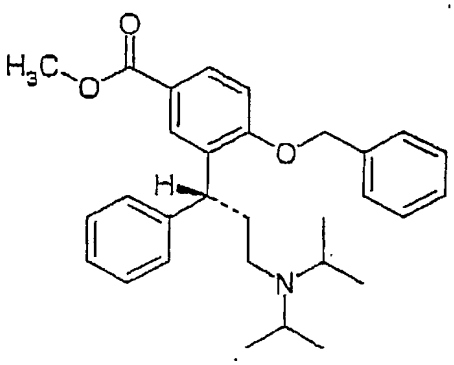
22. Use of a compound in accordance with claims 18 to 20 as an intermediate product in the manufacture of phenolic monoesters of general formula A



Formula A

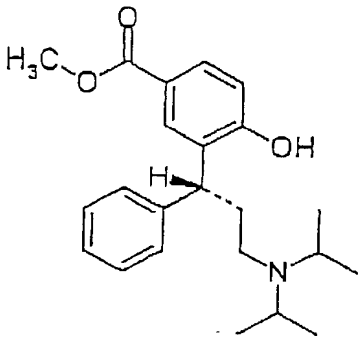
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl.

23. Compound of formula 3



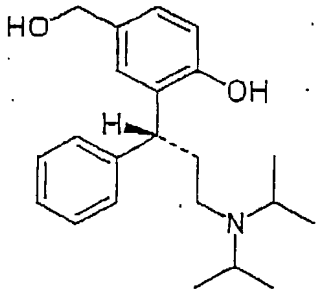
Formula 3

24. Compound of formula 5



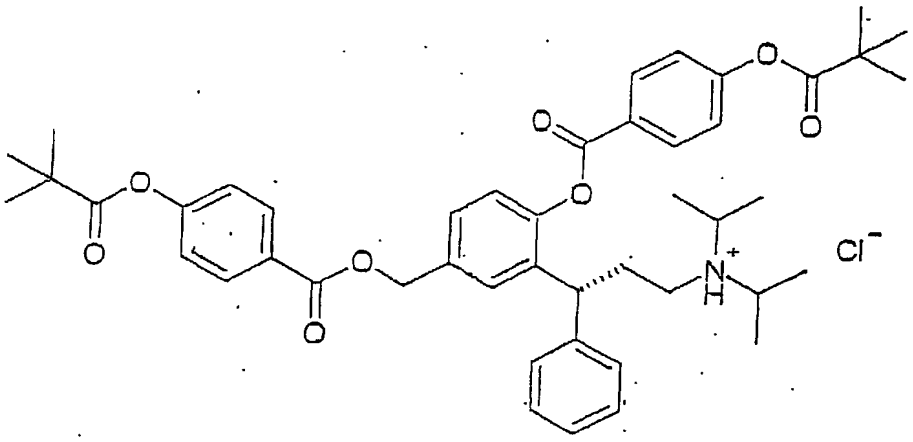
Formula 5

25. Compound of formula 6



Formula 6

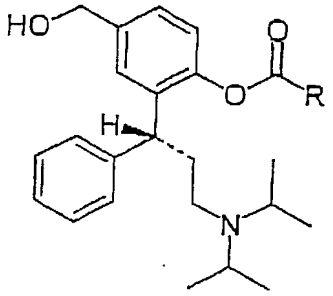
26. Compound of formula 7



Formula 7

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

29. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of salts of phenolic monoesters of general formula 2, in which R has the same meaning as given in claim 3.

30. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

ABSTRACT

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the manufacture and highly pure, stable intermediate products.

The method is in particular characterised by regio- and chemoselectivity and high yield. Salts of phenolic monoesters of 3,3-diphenylpropylamines are provided, that are particularly well-suited for use in pharmaceutical formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate. Furthermore, stable, crystalline intermediate products that are essential for obtaining the abovementioned salts are provided. A preferred intermediate product is *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

PTO/SB/01 (03-01)
Approved for use through 10/31/2002. OMB 0651-0032
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	Express Mail No.	
DECLARATION FOR UTILITY, DESIGN, DIVISIONAL AND CONTINUATION-IN-PART PATENT APPLICATIONS (37 CFR 1.63)	**Attorney Docket Number**	41946/32854
	First Named Inventor	MEESE, Claus
☒ Declaration Submitted with Initial Filing	***COMPLETE IF KNOWN***	
	Application Number	To be assigned
☐ Supplemental Declaration Submitted ☐ Declaration Submitted for Continuation-In-Part Filing ☐ Declaration Submitted for Divisional Filing	Filing Date	To be assigned
	Group Art Unit	To be assigned
	Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-PHENYLPROPYLAMINES

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 11/15/2000 as United States Application Number or PCT International Application Number PCT/EP00/11309 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
DE 199 55 190.1	Germany	11/16/1999	☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

1887648

10/130214
JC13 Rec'd PCT/PTO 14 MAY 2002

PTO/SB/96 (08-00)
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: SCHWARZ PHARMA AG

Application No./Patent No.:_____ Filed/Issue Date:_____

Entitled: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

SCHWARZ PHARMA AG, a CORPORATION,
(Name of Assignee) (Type of Assignee, e g , corporation, partnership, university, government agency, etc)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by, percentage) of its ownership interest is _____%

in the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From _____ To:_____
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Reel _____, Frame_____, or for which a copy thereof is attached.

2. From _____ To:_____
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3. From _____ To:_____
The document was recorded in the United States Patent and Trademark Office at
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[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

2 May 2002
Date

ppa. K.-D. Hommerich i.V. D.W. Schacht
Typed or printed name

Signature

Authorized Officer Assistant Manager
Title

Burden Hour Statement: This form is estimated to take 0 2 hours to complete. Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U S Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO. Assistant Commissioner for Patents, Washington, DC 20231.

1887451

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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Application Number	
Filing Date	
First Named Inventor	MEESE, Claus
Title	STABLE SALTS OF et al.
Group Art Unit	
Examiner Name	
Attorney Docket Number	41946/32854

I hereby appoint:

☒ Practitioners at Customer Number 021888 → Place Customer Number Bar Code Label Here 21888 PATENT TRADEMARK OFFICE

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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☐ The above-mentioned Customer Number

OR

☒ Practitioners at Customer Number 021888 → Place Customer Number Bar Code Label Here 21888 PATENT TRADEMARK OFFICE

OR

☒ Firm *or* Individual Name	Paul A. Lesko				
Address	Thompson Coburn LLP				
Address	One US Bank Plaza				
City	St. Louis	State	MO	Zip	63101
Country	USA				
Telephone	314-552-6443	Fax	314-552-7000		

I am the:

☐ Applicant/Inventor.

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	ppa. K.-D. Hommerich i.V. D.W. Schacht
Signature	
Date	2 May 2002

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

Burden Hour Statement This form is estimated to take 3 minutes to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

PTO/SB/01 (03-01)
Approved for use through 10/31/2002. OMB 0651-0032
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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ☒ Customer Number or Bar Code Label 021888 OR ☐ Correspondence address below

Name Paul A. Lesko, Esq.

Address Thompson Coburn LLP
One U.S. Bank Plaza, Suite 3500

City St. Louis **State** MO **ZIP** 63101

Country USA **Telephone** 314-552- 6443 **Fax** 314-552-7443

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Claus **Family Name or Surname** MEESE

Inventor's Signature Dr. Claus D. Meese **Date** 2 May 2002

Residence: City Monheim **State** DEX **Country** Germany **Citizenship** Germany

Mailing Address Kreuzbergerstrasse 50

City 40789 Monheim **State** **ZIP** **Country** GERMANY

NAME OF SECOND INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) **Family Name or Surname**

Inventor's Signature **Date**

Residence: City **State** **Country** **Citizenship**

Mailing Address

City **State** **ZIP** **Country**

☐ Additional inventors are being named on the ____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

1887648

FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF [redacted]ERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

		AT[redacted]EY'S DOCKET NUMBER **41946/32854**
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) New **10/130214**
INTERNATIONAL APPLICATION NO. **PCT/EP00/11309**	INTERNATIONAL FILING DATE **15 NOVEMBER 2000**	PRIORITY DATE CLAIMED **16 NOVEMBER 1999**

TITLE OF INVENTION
STABLE SALTS OF NOVEL DERIVATIVES OF 3,3,-DIPHENYLPROPYLAMINES

APPLICANT(S) FOR DO/EO/US
MEESE, Claus

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☒ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Certificate of Express Mailing;
    Postcard
    Statement Under 37 CFR 3.73(b)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
New 10/130214	PCT/EP00/11309	41946/32854

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	30- 20 =	10	x $18.00	$	180.00
Independent claims	10- 3 =	7	x $80.00	$	560.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	270.00
			TOTAL OF ABOVE CALCULATIONS =	$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
			SUBTOTAL =	$	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	40.00
			TOTAL FEES ENCLOSED =	$	1910.00
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1910.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-0823. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to review (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Paul A. Lesko, Esq.
Thompson Coburn LLP
One U.S. Bank Plaza
St. L uis, MO 63101
Telephone No.: 314.552.6443
Facsimile No.: 314.552.7000

Signature

Paul A. Lesko
Name

45,364
Registration Number

EXPRESS MAIL CERTIFICATE OF MAILING (37 CFR 1.10) Express Mail No. EL942731601US	Docket No. 41946/32854

In Re Application Of:
MEESE, Claus

Serial No.	Filing Date	Examiner	Group Art Unit
New 10/130274	Herewith	Not assigned	Not assigned

Title:
STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS

Transmitted herewith is:

- ☒ Transmittal Letter to the United States Designated/Elected Office (DE/EO/US) Concerning a Filing under 35 U.S.C. 371
- ☒ Declaration
- ☒ English Translation of the International Application as filed
- ☒ Preliminary Amendment
- ☒ Information Disclosure Statement
- ☒ Assignment and Recordation Form Cover Sheet
- ☒ Statement Under 37 CFR 3.73(b)
- ☒ Power of Attorney
- ☒ Check number 446161
- ☒ Postcard

Paul A. Lesko, Reg. No. 45,364
Thompson Coburn LLP
One U.S. Bank Plaza, Suite 3500
St. Louis, Missouri 63101
314-552-6443
314-552-7000 FAX

Customer No. 021888

I certify that the document and fee is being deposited on May 14, 2002 with the U.S. Postal Service as Express Mail under 37 C.F.R. 1.10 and is addressed to the Commissioner for Patents, Box PCT, Washington, D.C. 20231.

Express Mail No. EL942731601US

Signature of Person Mailing Correspondence

Paul A. Lesko
Typed or Printed Name of Person Mailing Correspondence

1895472

ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
	/		
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	/		^ Continued on Issue Slip Inside File Jacket

INDEX OF CLAIMS

✓ ..... Rejected – (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

Claim Final	Claim Original	Date
	1	7/2/03
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If more than 150 claims or 9 actions staple additional sheet here

10/130214

FILED UNDER 35 U.S.C. 371

PATENT NUMBER and ISSUE DATE

U.S. UTILITY Patent Application

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10130214	05/14/2002	~~514~~ 540	~~539~~ 539/19	~~1624~~ 1614	TUCKER Z

**APPLICANTS: Meese Claus;

**CONTINUING DATA VERIFIED:
THIS APPLICATION IS A 371 OF PCT/EP00/11309 11/15/2000

** FOREIGN APPLICATIONS VERIFIED:
GERMANY 199 55 190.1 11/16/1999

PG-PUB	DO NOT PUBLISH ☐	RESCIND ☐	
Foreign priority claimed	☐ yes ☐ no	ATTORNEY DOCKET NO	
35 USC 119 conditions met	☐ yes ☐ no	41946/32854	
Verified and Acknowledged Examiners's intials			

TITLE : Stable salts of novel derivatives of 3,3-diphenylpropylamines

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

NOTICE OF ALLOWANCE MAILED	Assistant Examiner	CLAIMS ALLOWED: Total Claims / Print Claim for O.G.
ISSUE FEE: Amount Due / Date Paid		DRAWING: Sheets Drwg. / Figs.Drwg. / Print Fig.
☐ TERMINAL DISCLAIMER	Primary Examiner / PREPARED FOR ISSUE	Application Examiner

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FILED WITH: ☐ DISK (CRF) ☐ CD-ROM (Attached in pocket on right inside flap)

SEARCH

Class	Sub.	Date	Exmr.
560	37, 42, 18, 140, 142	7/30/02	ZT
564	319		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
PALM INVENTOR NAME SEARCHED	7/30/03	ZT
STN REGISTRY, CAPLUS STRUCTURES SEARCHED IN REGISTRY x'd w/ CAPLUS: (TRANSCRIPT ATTACHED)	7/30/03	ZT

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number

10/130214

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	30	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	47 minus 20=	* 27
INDEPENDENT CLAIMS	10 minus 3 =	* 7
MULTIPLE DEPENDENT CLAIM PRESENT		☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	~~740.00~~ 890
X$ 9=		OR	X$18=	486
X42=		OR	X84=	588
+140=		OR	+280=	280
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

SMALL ENTITY OR OTHER THAN SMALL ENTITY

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PATENT APPLICATION SERIAL NO. 10/130214

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

05/22/2002 GFREY1 00000027 10130214

01 FC:970 890.00 OP
02 FC:966 180.00 OP
03 FC:964 588.00 OP

05/22/2002 GFREY1 00000027 10130214

05 FC:198 212.00 OP

Adjustment date: 08/02/2002 BCAMPBEL
05/22/2002 GFREY1 00000027 10130214
05 FC:198 -212.00 OP

08/02/2002 BCAMPBEL 00000005 200823 10130214

01 FC:968 68.00 CH 212.00 OP
02 FC:966 306.00 CH

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/130214 | FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
2		1		1		
3		(1)		(1)		
4		1		1		
5		(1)		(1)		
6		(1)		(1)		
7		(1)		(1)		
8	1		1			
9		1		1		
10	1		1			
11		1		1		
12		4		4		
13		4		4		
14		4		4		
15		(1)		(1)		
16		(1)		(1)		
17		(1)		(1)		
18	1		1			
19	1		1			
20	1		1			
21		3		(1)		
22		3		3		
23	1		1			
24	1		1			
25	1		1			
26	1		1			
27		4		(1)		
28		4		4		
29		(1)		(1)		
30		4		4		
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TOTAL IND.		⇦	10	⇦		⇦
TOTAL DEP.			37			
TOTAL CLAIMS			47			

	☆		☆		☆	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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99						
100						
TOTAL IND.		⇦		⇦		⇦
TOTAL DEP.						
TOTAL CLAIMS						

☆ *MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS*

Barbara Campbell
National Stamp Processing
(703) 305-3391

FORM PTO-1360 (REV. 3-78)

U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

#4/a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: MEESE, Claus et al.	)	**Examiner:** To be assigned
Application No.: To be assigned	)	**Group Art Unit:** To be assigned
Filed: Herewith	)	
Title: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES	)	**Docket No.:** 41946/32854

Commissioner for Patents
Box PCT
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the filing fee and examination on the merits, kindly amend the above-identified patent application per the following instructions.

Kindly amend the specification at page one after the title and before the first line of text, by inserting at that point the following sentence --This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

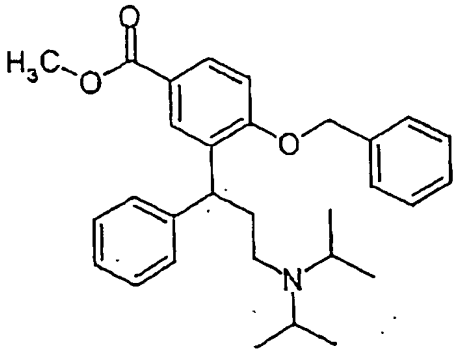
a'

The amendments to claims 18-21, 23-25, 27, and 28 are pursuant to an Article 34 amendment made to the PCT application on October 5, 2001.

IN THE CLAIMS

At page 56, amend claims 18-21, 23-25, 27, and 28 as follows:

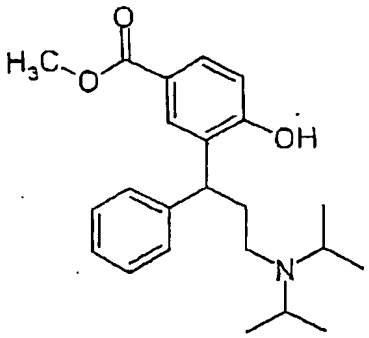
18. (once amended) Compound of formula III



Formula III

in highly pure, crystalline and stable form.

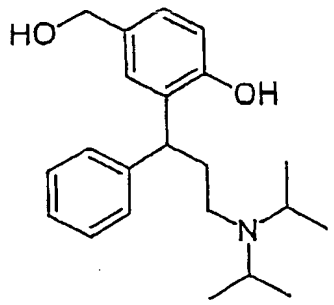
19. (once amended) Compound of formula V



Formula V

in highly pure, crystalline and stable form.

20. (once amended) Compound of formula VI

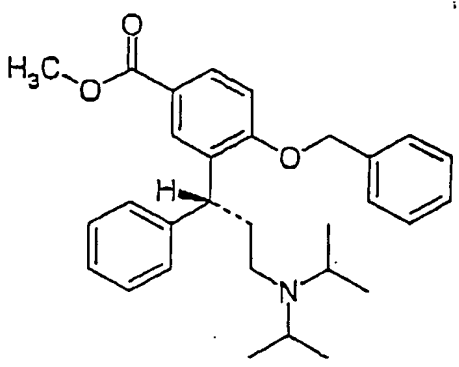


Formula VI

in highly pure, crystalline and stable form.

21. (once amended) Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

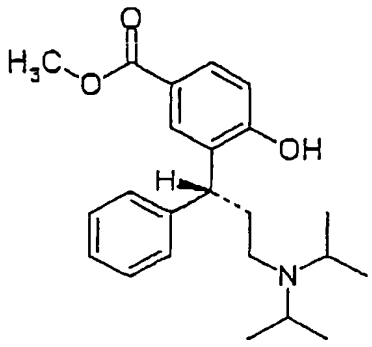
23. (once amended) Compound of formula 3



Formula 3

in highly pure, crystalline and stable form.

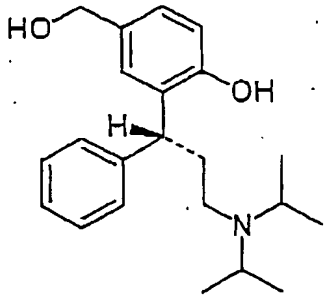
24. (once amended) Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. (once amended) Compound of formula 6

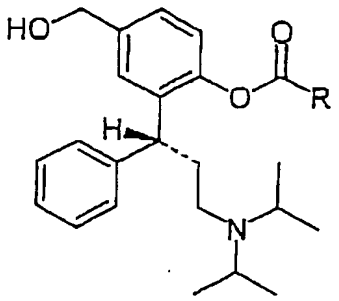


Formula 6

in highly pure, crystalline and stable form.

27. (once amended) Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. (once amended) Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Kindly consider this preliminary amendment and enter it into the record of this application. Attached is a clean copy of the claims. All correspondence should to be directed to Paul A. Lesko, Thompson Coburn LLP, One U.S. Bank Plaza, St. Louis, MO 63101, Telephone No.: 314.552.6443, Facsimile No.: 314.552.7000.

Respectfully submitted,

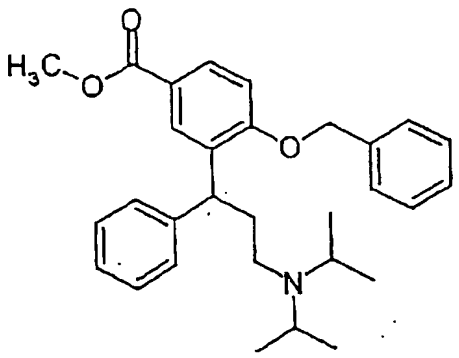
Paul A. Lesko
Registration No. 45,364
Thompson Coburn LLP
One U.S. Bank Plaza
St. Louis, MO 63101
Telephone: 314.552.6443
Facsimile: 314.552.7000

CLEAN COPY OF PARAGRAPH TO BE INSERTED INTO SPECIFICATION

-- This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

18. Compound of formula III

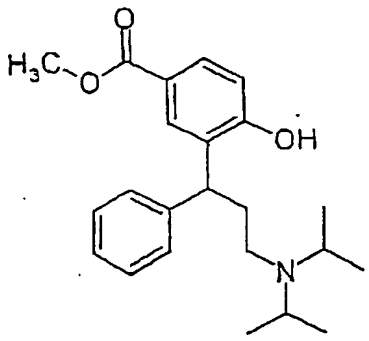
a 2



Formula III

in highly pure, crystalline and stable form.

19. Compound of formula V

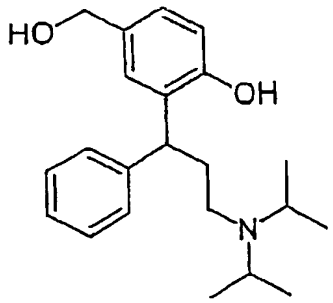


Formula V

in highly pure, crystalline and stable form.

20. Compound of formula VI

Q2



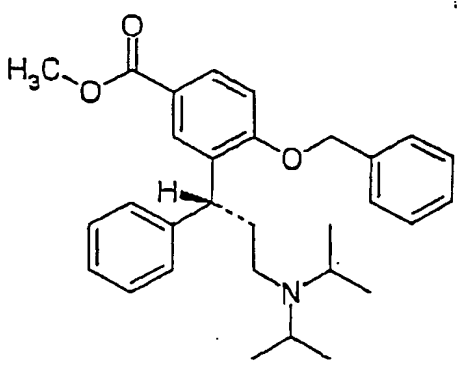
Formula VI

in highly pure, crystalline and stable form.

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

23. Compound of formula 3

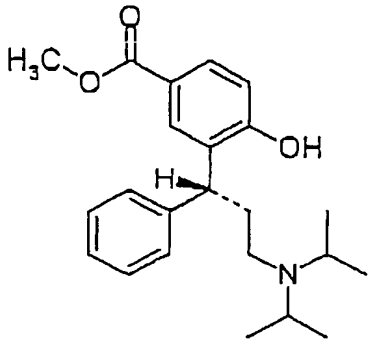
Q3



Formula 3

in highly pure, crystalline and stable form.

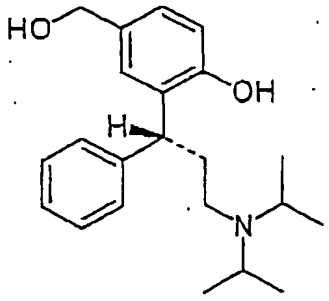
24. Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. Compound of formula 6

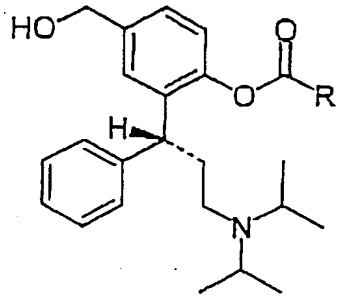


Formula 6

in highly pure, crystalline and stable form.

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



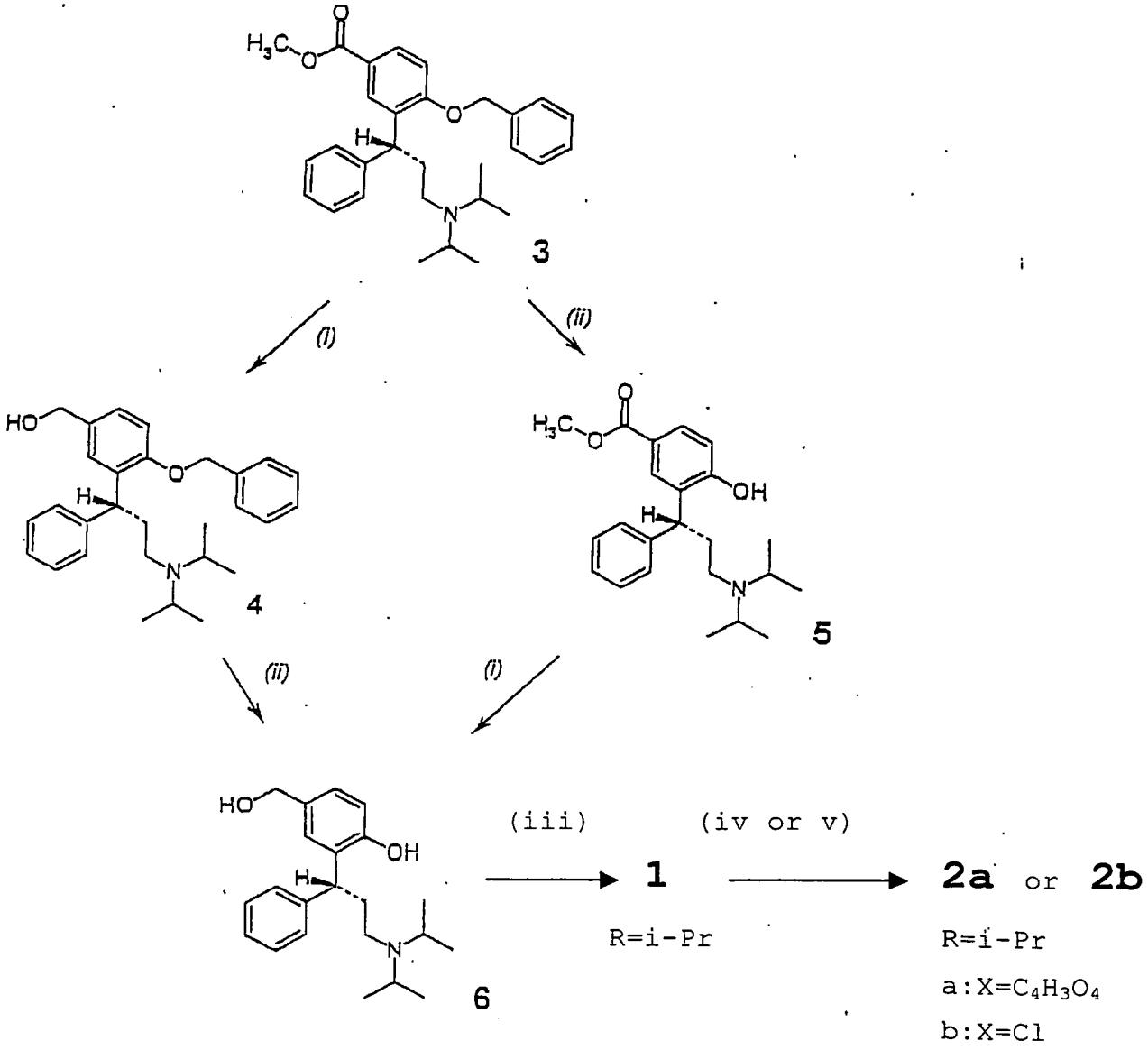
Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



SPECIFICATION

Stable salts of novel derivatives of 3,3-diphenylpropylamines

ins a'

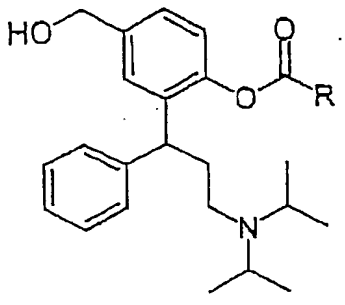
The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugs for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourable metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylamines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below



Formula A

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

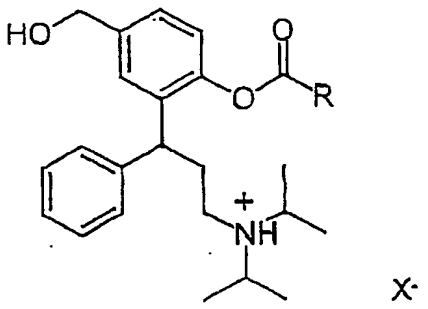
Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification.

During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

Basically salts of the compounds of general formula A can be obtained if solutions of the compounds of formula A (base component) are purified with solutions of acids in suitable solvents, but the salts obtained in the form of solid matter can prove to be altogether amorphous and/or hygroscopic and cannot be directly crystallized from the normal solvents either. Such salts have inadequate chemical stability to be galenically processed as valuable pharmaceutically active substances.

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been prepared under a special reaction process, are converted with a physiologically compatible inorganic or organic acid with general formula H-X, in which ^-X represents the respective

acid residue, into their respective salt with general formula I.



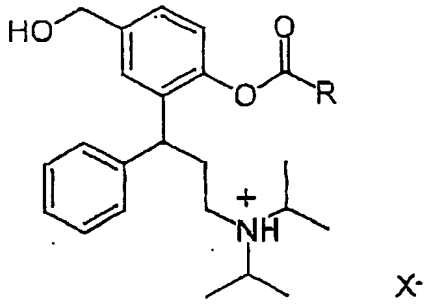
Formula I

The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

A further problem for the present invention is to provide a method for manufacturing such highly pure, crystalline, stable compounds in the form of their salts, as well as highly pure, stable intermediate products.

The final problem for the invention is to provide a method for manufacturing the abovementioned compounds with which a high yield of the products of the process and the respective intermediate products can be obtained chemo- or regioselectively.

This problem is solved in that highly pure, crystalline, stable compounds of the 3,3-diphenylpropylamines in the form of their salts with general formula I are provided,



Formula I

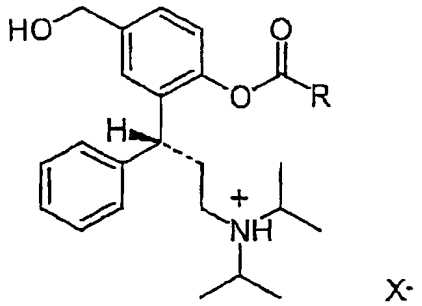
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with a design of the invention the salts of general formula I can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid

(3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

In accordance with a further design form of the invention *R*-configured compounds with general formula 2 are provided



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with an advantageous design form of the invention the compounds in the form of their salts of general formula 2 can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-

glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate

- and

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Furthermore, compounds are preferred in which R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

Particular preference is for [(R)-3-(2-{1-[4-(1-cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenylpropyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-

propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride and {(R)-3-[2-(1-cyclohexyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride.

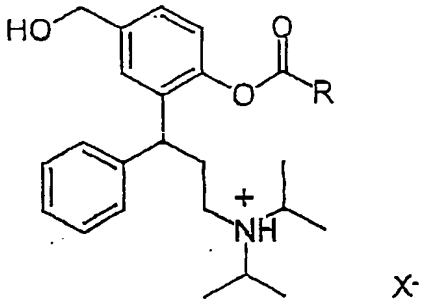
In the compounds of the present invention the expression "alkyl" preferably stands for a straight-chain or branched-chain hydrogen group with between 1 and 6 C-atoms. Special preference is for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The expression "cycloalkyl" designates cyclical hydrogen groups, that have between 3 and 10 hydrogen atoms, that may also contain suitable substitutes in place of the hydrogen atoms.

The expression "phenyl" designates a $-C_6H_5$-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable halogens are fluorine, chlorine, bromine and iodine atoms

The present invention also includes methods for manufacturing the compounds in accordance with the invention of general formula I as well as valuable intermediate products.

The method is characterised by chemo- and regioselectivity.

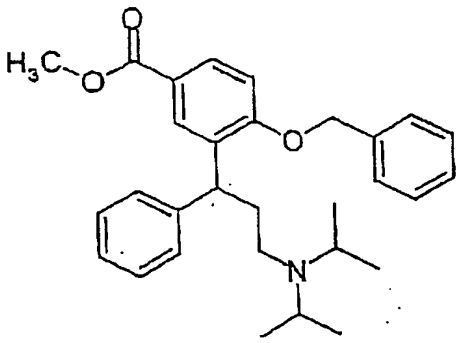
Compounds of general formula I



Formula I

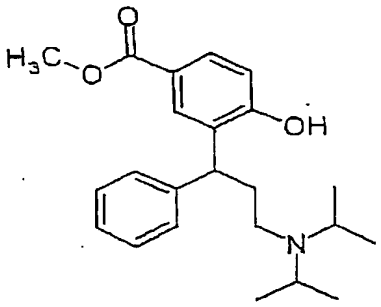
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are manufactured in that

a) a compound of formula III



Formula III

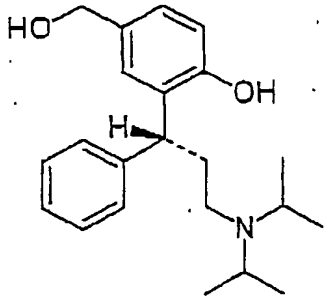
is split with a hydrogenation agent to form a compound of formula V



Formula V

whereupon

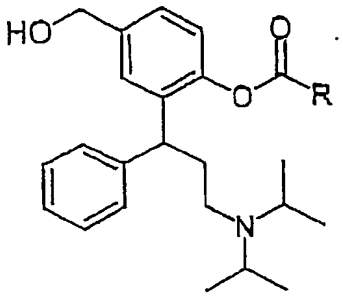
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

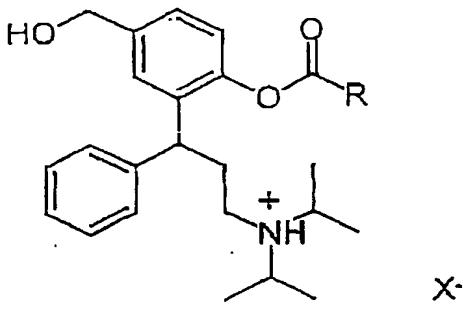
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

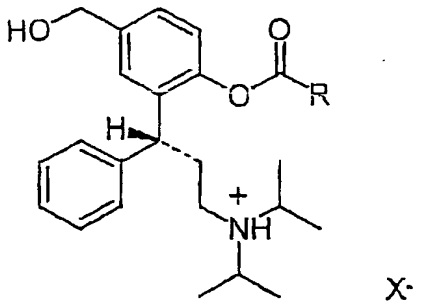


Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with the invention, for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

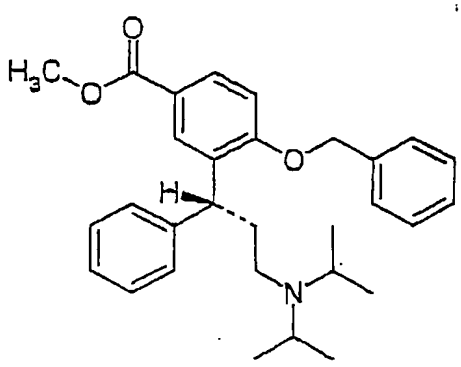
In accordance with an advantageous further development of the invention a method for the manufacture of *R*-configured compounds of the general formula 2 is described,



Formula 2

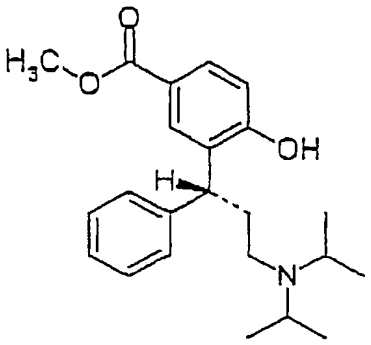
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, in that

a) a compound of formula 3



Formula 3

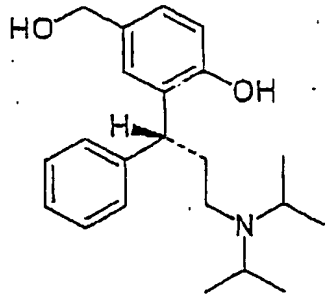
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

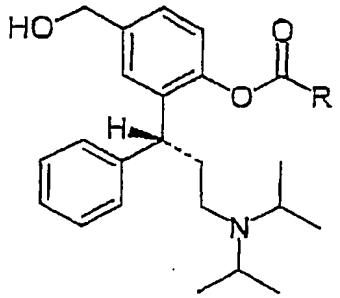
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

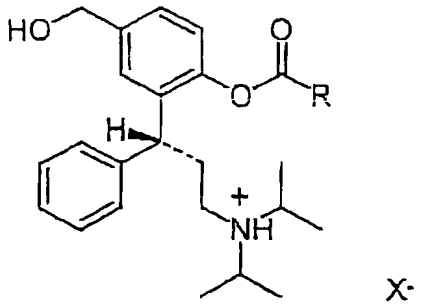
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

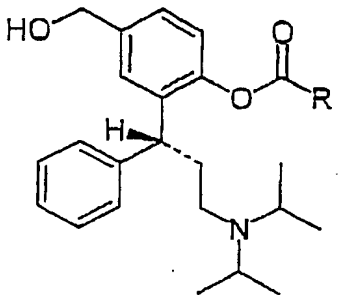
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

Advantageously in order to obtain compounds of general formula 2, in accordance with the method hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Particular advantageously, on the basis of the crystalline *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)benzoic acid methyl ester, the highly pure,

crystalline intermediate product *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester is prepared, which is reduced to *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, is finally acylated in a suitable manner and is then converted with a physiologically compatible inorganic or organic acid under spontaneous crystallisation to the respective highly pure, crystalline, stable salt.

Depending on the acid chloride used, compounds of general formula 1 are obtained,



Formula 1

in which R denotes C_1-C_6-alkyl, in particular isopropyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

In order to obtain the compounds in accordance with the invention in the form of their salts the special reaction process via particular intermediate stages and individually identifiable intermediate products is crucial.

This is explained using reaction diagram 1 (see Figure 1), in which the conversions with *R*-configured compounds are described, but without this being restrictive.

In this:

3 = *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid- methyl ester

4 = *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5 = *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

6 = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1 = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester

2a = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl-isobutyrate ester hydrogen fumarate

2b = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydro xymethylphenyl-isobutyrate ester hydrochloride hydrate

In accordance with the reaction process explained in the embodiment the preliminary stage 3 (*R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methylester) is prepared in crystalline, pure form.

Using normal methods – such as BBr_3, $AlCl_3$ – but preferably by means of hydrogen gas via Raney nickel in methanol as the solvent at room temperature (RT), preliminary stage 3 is split into 5 (*R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methylester. This develops in highly pure, crystalline form (melting point 143.7 °C).

Finally, using a suitable reducing agent – such as $NaBH_4$/EtOH – preferably $LiAlH_4$ 5 is reduced into an inert solvent at low

temperature (-78°C to + 10°C) and the compound 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) is obtained. The compound 6 is obtained in a highly pure state and can be crystallised from a suitable solvent such as ethyl acetate. The colourless, compact grained material has a melting point of 102.3°C. This is surprising in that the compound 6 in the state of the art is described as an amorphous solid.

Compound 6 is now acylated with very good yield and regio- and chemoselectivity, into a phenolic ester. This reaction is performed at RT or low temperatures with an equivalent acid chloride in the presence of a base in a suitable solvent. Suitable solvents are ethyl acetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene.

The reaction is preferably performed with isobutyrylchloride as the acid chloride and triethylamine as the base at the abovementioned temperatures. The 1 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester) then obtained, occurs with such purity that with solutions of the fumaric acid in suitable solvents spontaneous crystallisation starts with the formation of the hydrogen fumarate salt 2a.

This salt has a high melting point of 103°C, is stable at RT, is non-hygroscopic and does not contain crystallose agents. It can be recrystallised as often as desired.

If instead of fumaric acid anhydrous hydrochloric acid is used - for example as an etheric solution - salt formation also takes place with the crystalline product 2b (*R*-(+)-2-(3-

diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate being obtained.

Following a further recrystallisation the product 2b has a melting point range of 97 - 106°C.

Finally the product 2b can particularly advantageously be obtained by the following variants of the inverse reaction process, starting with the compound 6 of reaction diagram 1. The product 2b can thus be obtained without the addition of an external acid-intercepting base, as explained in the following.

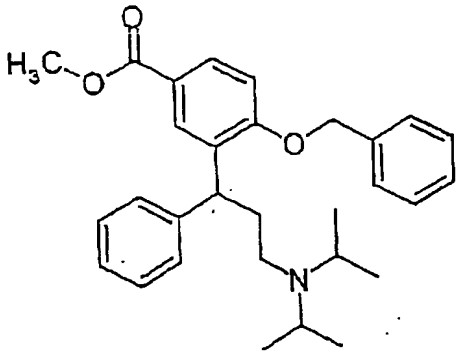
Solutions of 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) are dripped into solutions of isobutyrate chloride, so that under suitable polarity conditions the anhydrous product 2b rapidly crystallises out. 2b is very hygroscopic.

If the abovementioned reaction is carried out in a humid solvent, that contains at least one mole equivalent of water, a stable and crystalline, hydrate-containing product 2b is obtained, that has the abovementioned melting characteristics.

The compounds in accordance with the invention of general formulae 1 and 2 are suited to bulk material.

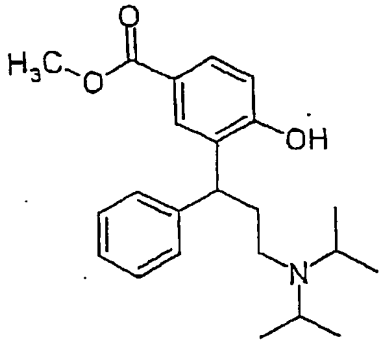
Of particular advantage are the highly pure compounds of general formulas III, V, VI, 3, 5, 6 and 7 which can be obtained.

Compound of formula III



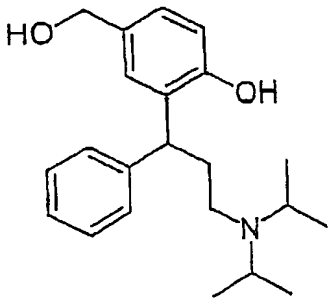
Formula III

Compound of formula V



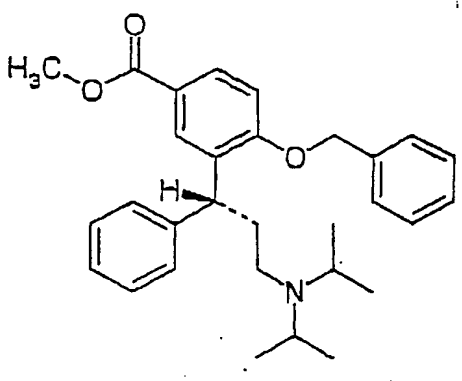
Formula V

Compound of formula VI



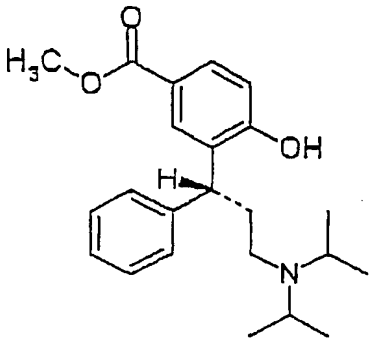
Formula VI

Compound of formula 3



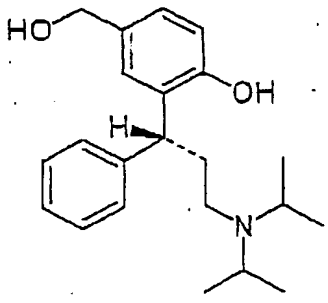
Formula 3

Compound of formula 5



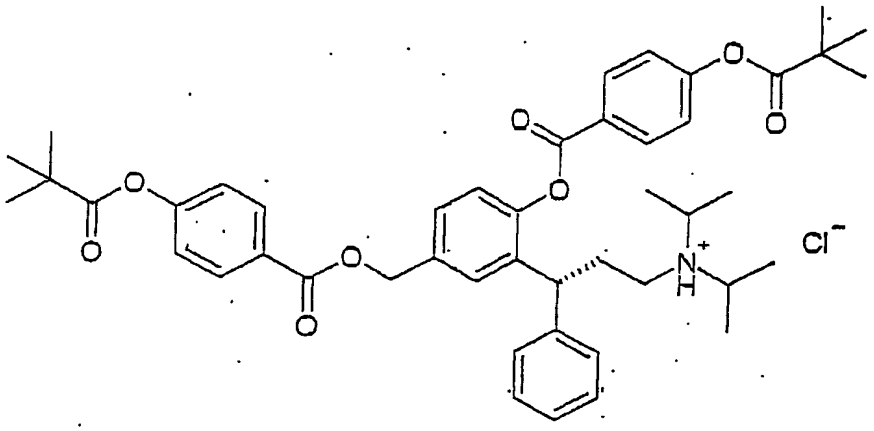
Formula 5

Compound of formula 6



Formula 6

Compound of formula 7



Formula 7

[(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methaneoyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methaneoyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chloride

The abovementioned compounds III, V, VI, 3, 5, 6 and 7 are particularly suited to use in each case as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

Of particular advantage are compounds for use as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Finally, the method can be carried out in a particularly advantageous way by converting a compound of general formula 6 (see reaction diagram 1) with an equivalent isobutyryl

chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester.

In accordance with the invention *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is particularly suited to conversion with fumaric acid or hydrochloric acid with the formation of the respective salt.

The following embodiments explain the invention.

Experimental

I. General

All compounds have been fully characterised by ^{1}H and ^{13}C NMR-spectroscopy (Bruker DPX 200). The stated chemical displacements in the ^{13}C-NMR-spectra (50 MHz, ppm values stated) refer to the solvent resonances of $CDCl_3$ (77.10 ppm). ^{1}H NMR data ($CDCl_3$; 200 MHz, ppm) refer to internal tetramethylsilane).

Thin layer chromatography (DC, R_f given) was carried out on 5x10 cm E. Merck silica gel films (60F254), and the stains were revealed by fluorescence erasure or by spraying with alkaline potassium permanganate solution.

Absorbent systems were: (1), n-hexane / acetone / triethylamine (70/20/10, v/v-%); (2), toluene / acetone / methanol / acetic acid (70/5/20/5, v/v-%).

The optical rotations were measured at a wavelength of 589.3 nm (sodium D-line), at room temperature using ethanol as a solvent (apparatus: Perkin Elmer Polarimeter Type 241), melting points (in °C) are uncorrected and were determined on the Mettler FP apparatus, or by differential thermoanalysis (DSC) on the Perkin Elmer Model DSC7, using "Pyris" evaluation software.

UV/VIS measurements were carried out on the spectrophotometer model Lambda 7 (Perkin-Elmer) with a layer thickness of 1 cm. The specific absorption stated is for a 1% solution ($A^{1\%}_{1\ cm}$).

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer Series 1610 (resolution 4 cm^{-1}).

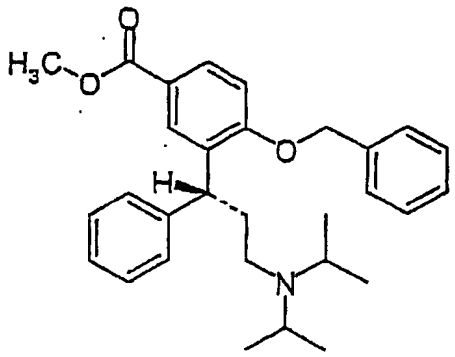
Gas chromatography mass spectrometry (GC-MS, m/z values and relative intensity with reference to the base ion (%)) was carried out with a Finnigan TSQ 700 Triple Mass Spectrometer in positive (P-CI) or negative (N-CI) chemical ionisation measurement mode with methane or ammonium as a reactant gas or via electron impact ionisation. Hydroxy compounds were measured as trimethylsilylether-derivatives.

Coupled liquid chromatography-mass spectrometry (LC-MS): Waters Integrity System, Thermabeam Mass Detector (EI, 70 eV), m/z-values and relative intensity (%) are given over a quantity range of 50-500 a.m.u.

II. Embodiments

The Arabic numerals in brackets (3), (4), (5), (6) refer to the identical designations in reaction diagram 1.

1. Preparation of
R-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methylester (3)



A solution of *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid hydrochloride (2.30 kg, 4.77 Mol) in 26.4 litres of methanol and 0.25 litre of concentrated sulphuric acid is heated for 16 hours with recycling. Then a third of the solvent is distilled off, cooled and under agitation mixed with 5 kg ice and 2.5 litres 25% aqueous sodium carbonate solution. The deposit is first extracted with 15 litres and then again with 5 litres of dichloromethane. The organic phases are purified and concentrated on the rotary evaporator until dry. 1.99 kg (90.7% of theoretical) dark yellow oil with a purity of approximately 90% (DC, NMR) are obtained.
DC (1): 0.58

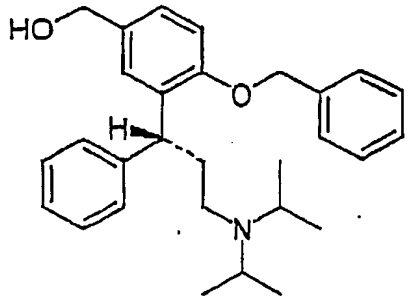
^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.83, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22,129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Recrystallisation

69.0 oily raw material is dissolved in 150 ml boiling methanol. Following the addition of 15 ml distilled water it is left at 0°C, whereupon colourless crystals precipitate. These are filtered off, washed with a little cold methanol and vacuum-dried. Yield: 41.8 g (60.6 % of theoretical) colourless crystals, melting point 89.8 °C; $[I]_D^{20}$ = - 30.7 (c = 1.0, ethanol).

2. Preparation of

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)



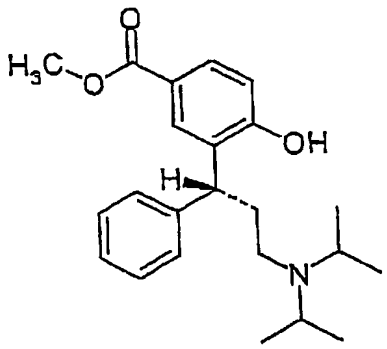
Raw product (3) (28 g) is dissolved in 230 ml pure diethylether and under agitation is dripped into a suspension of 1.8 g lithium-aluminium hydride in diethylether (140 ml). After 18 hours of agitation at room temperature, 4.7 ml of water are added in drop form. The organic phase is separated

off, dried with anhydrous sodium sulphate, filtered and concentrated on the rotary evaporator until dry. 26 g (98.9% of theoretical) *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) are obtained as a colourless oil.

DC (2): 0.32; $[I]_D^{20}$ = + 6.3 (c = 1.0, ethanol).

^{13}C-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.

3. Preparation of *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5)



To an agitated suspension of 5g Raney nickel (washed with water, then with methanol) in 200 ml methanol, 10 g (21.8 mmol) *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl ester (3) are added. Following brief heating, in order to dissolve all (3) completely, the apparatus is placed under a hydrogen gas atmosphere. After three hours of agitation at normal pressure and room temperature, the thin layer chromatography demonstrates

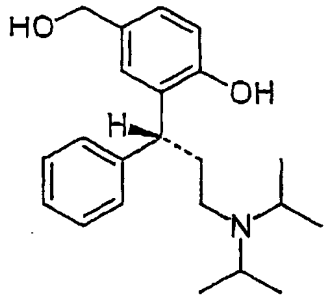
complete conversion. The deposit is rinsed with nitrogen gas and following addition of some active charcoal is filtered. Following concentration of the methanolic solution on the rotary evaporator 6.0 g (75% of theoretical) *R*-(-)-3-(3-diisopropylaminophenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5) remains in the form of colourless crystals with a purity of 99.6 % (HPLC).

Melting point 143.7 °C; DSC 144.7°C

$[I]_D^{20}$ = -26.6 (c = 0.93, ethanol).

^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Starting from the intermediate stage (4), *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) are dissolved in 220 ml methanol and Raney nickel (5 g). The apparatus is rinsed with hydrogen gas and the deposit is agitated for two days at room

temperature. Following the addition of a further 5 g Raney nickel, agitation for a further two days at room temperature takes place under a hydrogen gas atmosphere, followed by filtration off from the catalyser and concentration until dry on the rotary evaporator. The oily, pale yellow residue is dissolved in 100 ml diethylether, washed twice with 100 ml water each time, dried via sodium sulphate, filtered and concentrated until dry. 14.1 g (90.4% of theoretical) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol are obtained in the form of a cream-coloured, amorphous solid. For recrystallisation see under c).

b) Starting from the intermediate stage (5); *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

A solution of 370 mg (1.0 mmol) *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester in 20 ml anhydrous tetrahydrofurane is slowly and at room temperature dropped into an agitated mixture of dried tetrahydrofurane (10 ml) and a 1M solution of lithium-aluminium hydride in tetrahydrofurane (3 ml) (under a nitrogen protective gas atmosphere). Excess hydride is decomposed by the dropped addition of a saturated sodium carbonate solution. Following separation of the organic phase this is concentrated on the rotary evaporator and then dried in the high-vacuum. 274 mg (74% of theoretical) pale yellow oil is obtained, that slowly solidifies into an amorphous mass.

c) Recrystallisation:

Raw product 6 (1.0 g) is dissolved in ethyl acetate and again concentrated on the rotary evaporator. The diol released in

this way from foreign solvents (diethyl ether or tetrahydrofurane, see above) has 1.5 ml ethyl acetate added with slight heating. Agitation takes place until a clear solution results, followed by cooling at room temperature and addition of a few seed crystals. These are obtained by purifying raw 6 via HPLC, collecting the main fraction, concentrating this and drying the residue for a number of hours in the high-vacuum. Once clear crystallisation has definitely started, it is left at - 10°C. The crystals are sucked off in the cold and dried in the vacuum. Colourless crystals with a yield of 84% are obtained.

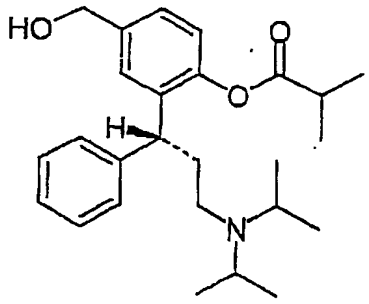
Melting point 102.3 °C

DC (1): 0.57

$[I]_D^{20}$ = +21.3 (c = 1.0, ethanol).

^{13}C-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.

5. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenolisobutyrate ester (1)

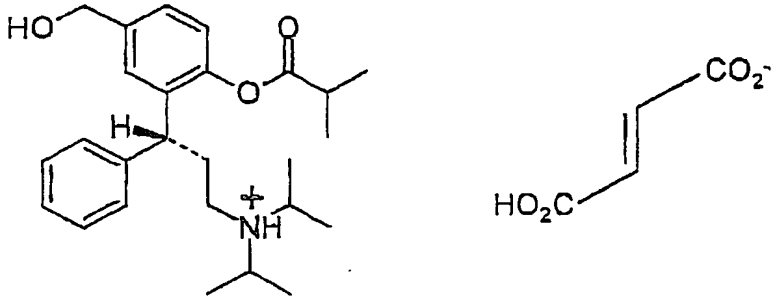


A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) and triethylamine (20.4 g, 201.7 mmol) in 750 ml dichloromethane has a solution of isobutyrate chloride (23.4 g, 201.7 mmol) in 250 ml dichloromethane added under agitation and cooling. Following addition agitation takes place for a further 15 minutes at 0°C, then for 30 minutes at room temperature and then one after another washing with water (250 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic phase is separated and concentrated on the rotary evaporator until dry. The ester *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is obtained as a colourless, viscous oil; yield: 77.1 g (98.4 % of theoretical).

DC (1): 0.26; $[I]_D^{22}$ = + 2.7 (c = 1.0, ethanol).

^{13}C-NMR ($CDCl_3$):19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125.59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.



A solution of 41.87 g (102 mmol) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester in 90 ml 2-butanone has fumaric acid (11.81 g, 102 mmol) added while heating. Following dissolution of the acid, cyclohexane (20-30 ml) is slowly added under agitation until the onset of turbidity. The colourless, homogenous deposit is initially left for 18 hours at room temperature, and then for several hours at 0°C. The colourless crystals that have precipitated are sucked off, washed with a little cyclohexane/2-butanone (90:10, vol.-%)and dried in the vacuum at 30°C. 44.6 g (83.1 % of theoretical) hydrogen furate salt of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester in the form of colourless flakes are obtained.

Melting point 98.8°C, a second crystallisation from the same solvent mixture provides a product with a melting point of 103°C.

$[I]_D^{20}$ = +6.0 (c = 1.0, ethanol).

Elementary analysis: Calculated for $C_{30}H_{41}NO_7$ (molecular weight 527.66) C 68.29 %, H 7.83 %, N 2.65 %, O 21.2 %; found C 68.29 %, H 7.90 %, N 2.72 %, O 21.0 %.

UV/VIS at Σ in nm ($A^{1\%}_{1\ cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

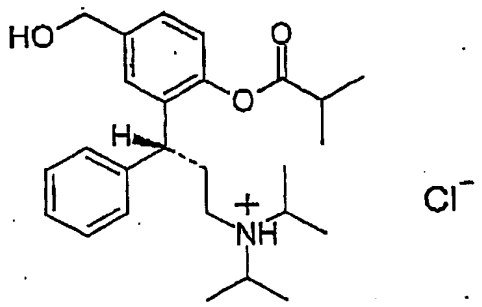
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 ($\underline{C}H_2OH$); 6.832 (=CH, fumarate); 6.84-7.62 (aryl, = CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CH\underline{C}H_2$); 34.09 ($\underline{C}H$-C=O); 41.87 ($CH\underline{C}H_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, fumarate); 170.48 (C=O, fumarate); 175.62 (i-Pr-C=O).

MS in the direct inlet, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrochloride hydrate



A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester (8.54 g, 25.0 mmol) in 50 ml dichloromethane is slowly dropped at 0°C into an agitated solution of isobutyrate chloride (2.66 g, 25.0 mmol) in 100 ml dichloromethane. After an hour the cooling is

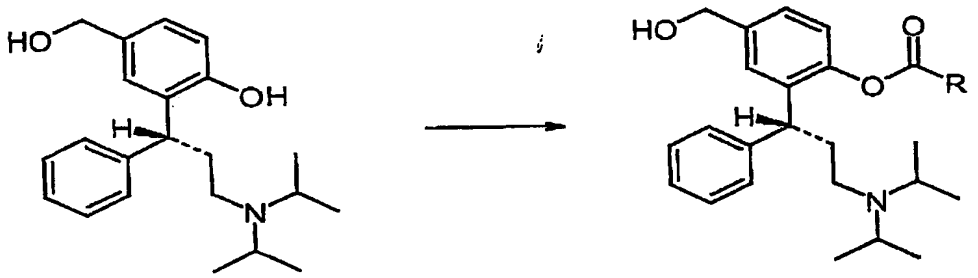
removed and re-agitation takes place for an additional hour. Following the drawing off of the volatile components in the vacuum on the rotary evaporator a colourless, amorphous-solid foam remains. This residue is dissolved in acetone (17 ml), with 0.45 to 0.50 g water and diethyl ether is added (approx. 20 - 25 ml) until there is a definite onset of turbidity. Following brief treatment with ultrasound crystallisation starts spontaneously and under agitation a further 80 ml of diethyl ether are slowly added. The precipitated colourless crystals are sucked off and dried overnight in the vacuum via phosphorous pentoxide. 10.5 g (93.7 % of theoretical) colourless crystalline *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate with a purity of 97.0% (HPLC) are obtained.

Melting point 97.1 °C.

$[I]_D^{20}$ = + 4.3 (c = 1.03, ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolic monoester



General work specification for the manufacture of phenolic monoesters

Into a solution of 120.3 mg (0.352 mmol) R-(+)-2-(3-diiso-propylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (0.352 mmol) in 2 ml dichloromethane is dropped. Then triethylamine-dichloromethane (49.1µl/0.353 mmol-2 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with 5 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = $CH_2CH(CH_3)_2$

R-(+)-3-methylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester

Colourless oil with 70% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.
DC (1): 0.76.

R = $CH_2C(CH_3)_3$

R-(+)-3.3-dimethylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base

Colourless oil with 69.7% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.
DC (1): 0.75.

R = $(CH_3)_3C$

R-(+)-3-pivalic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless crystals, melting point 165-6 °C.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R = c-C_3H_5

R-(+)-cyclopropane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35, 129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R = c-C_4H_7

R-(+)-cyclobutane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R = c-C_5H_9

R-(+)-cyclopentane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R = c-C_6H_{11}

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm):
174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R = 4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-ethylcarbonyloxy-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless crystals, melting point 195-8 °C.
^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.0 Hz, 1H, Phenyl-H3), 7.41-7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.6 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.97-2.74 (m, 2H, CH_2), 2.67 (q, J = 7.4 Hz, 2H, CH_2), 2.56-2.43 (m, 2H, CH_2), 1.23-1.13 (m, 15H, 2 × CH(C<u>H</u>$_3)_2$, CH_3).

R = 4-(i-$C_3H_7CO_2$)-C_6H_4

R-(+)-4-(isopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 202-4 °C.
^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.4 Hz, 1H, Phenyl-H3), 7.42-7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 2.99-2.78 (m, 3H, CH_2, $C\underline{H}(CH_3)_2$), 2.54-2.47 (m, 2H, CH_2), 1.29-1.13 (m, 18H, 3 × $CH(C\underline{H}_3)_2$).

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-(+)-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base.

Colourless oil.
^{1}H-NMR (DMSO-d_6): 8.19-8.12 (m, 2H, phenyl-H), 7.45-7.33 (m, 3H, phenyl-H), 7.25-7.09 (m, 7H, phenyl-H), 5.20 (t, J = 5.6 Hz, 1H, OH), 4.50 (d, J = 5.6 Hz, 2H, CH_2), 4.20 (t, J = 7.5 Hz, 1H, CH), 2.95-2.80 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 2.38-2.25 (m, 2H, CH_2), 2.09-2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82-0.76 (m, 12H, 2 × $CH(C\underline{H}_3)_2$).

Hydrochloride: colourless crystals, melting point 165-6 °C.
^{1}H-NMR ($CDCl_3$): 8.22-8.16 (m, 2H, phenyl-H), 8.02 (d, J = 1.8 Hz, 1H, phenyl-H), 7.27-7.02 (m, 9H, phenyl-H), 4.83-4.60

('m', 2H, CH_2), 4.01-3.94 (m, 1H, CH), 3.66-3.54 (m, 2H), 3.18-2.80 (m, 3H), 2.53-2.44 (m, 1H) (2 × CH_2, 2 × $C\underline{H}(CH_3)_2$), 1.43-1.25 (m, 21H, $(CH_3)_3$, 2 × $CH(C\underline{H}_3)_2$).

R = 4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(cyclopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 208-213 °C.
^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H can be substituted with D_2O, NH), 8.15-8.09 (m, 2H, phenyl-H), 7.53 ('d', 1H, phenyl-H3), 7.42-7.13 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.53 (m, 2H, 2 × $C\underline{H}$(CH3)2), 3.05-2.70 (m, 2H, CH2), 2.51-2.37 (m, 2H, CH2), 2.01-1.89 (m, 1H, cyclopropyl-CH), 1.20-1.05 (m, 16H, 2 × CH($C\underline{H}$3)2, 2 × cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R = 4-(c-$C_4H_7CO_2$)-C_6H_4

R-(+)-4-(cyclobutylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

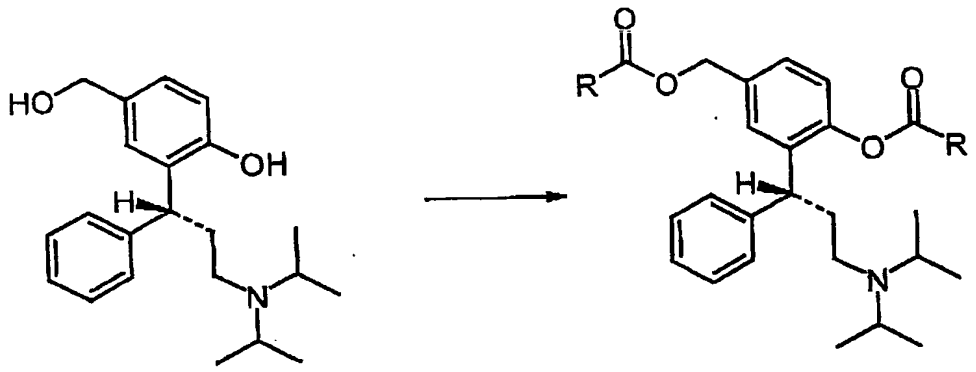
Colourless crystals, melting point 201-6 °C.
^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H can be substituted with D_2O, NH), 8.17-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.42-7.14 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.47 (m, 3H, cyclobutyl-CH), 2 × $C\underline{H}(CH_3)_2$), 3.00-2.70 (m, 2H, CH_2), 2.51-2.26 (m, 6H, CH_2, 2 × cyclobutyl-CH_2), 2.10-1.85 (m, 2H, cyclobutyl-CH_2), 1.22-1.12 (m, 12H, 2 × $CH(C\underline{H}_3)_2$).

R = 4-(c-$C_6H_{11}CO_2$)-C_6H_4

R-(+)-4-(cyclohexylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 212-217 °C.
^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, *can be substituted with D_2O*, NH), 8.16-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.39-7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, *can be substituted with D_2O*, OH), 4.53 (d, J = 4.2 Hz, 2H, CH_2), 4.22 (t, J = 7.5 Hz, 1H, CH), 3.62-3.48 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 3.00-2.60 (m, 3H, cyclohexyl-CH), CH_2), 2.51-2.40 (m, 2H, CH_2), 2.07-1.98 (m, 2H, cyclohexyl-CH_2), 1.80-1.11 (m, 20H, 4 × cyclohexyl-CH_2), 2 × $CH(C\underline{H}_3)_2$)

9. **Identical diesters**



General work specification for the manufacture of identical diesters

Into a solution of 7.30 g (21.4 mmol)R-(+)-2-(3-diiso-propylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (49.2 mmol) in 50 ml dichloromethane is dropped. Then triethylamine-dichloromethane (6.86 ml/ 49.2 mmol-50 ml)is added. After 1-3 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 100 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = Methyl

R-(-)-acetic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, free base

Pale yellow oil, purity (HPLC): 95.2%.
^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.
LC-MS: 425 (15%, $M^{+\cdot}$), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).
$[\alpha]_D^{20}$ = -33.1 (c = 1, CH_3CN).
DC (1): 0.79.

R = Cyclohexyl

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Pale yellow oil, purity (NMR): >95%.
^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.
DC (1): 0.96.

R = Isopropyl

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Free base: pale yellow oil, purity (HPLC): 95.6%.
^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.
DC (1): 0.74.

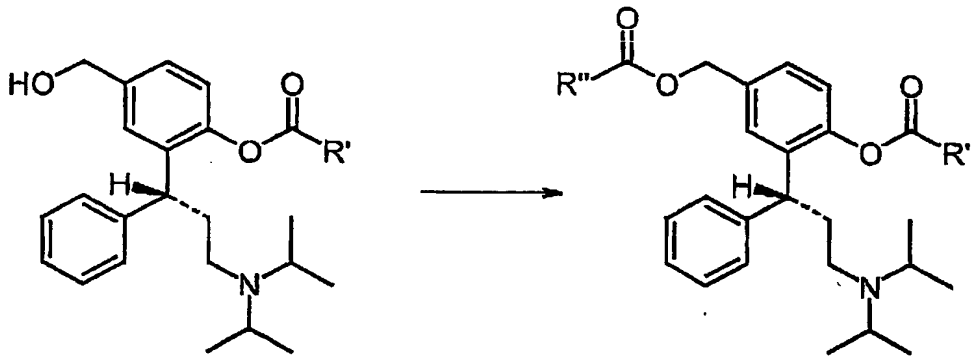
Hydrogen fumarate salt: colourless syrup, 94.4% HPLC purity.
^{13}C-NMR ($CDCl_3$): 17.89,
18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoic acid)-phenyl-ester hydrochloride

Colourless crystals, melting point 105-7 °C.
^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Mixed diesters



R` is not equal to R``

General work specification for the manufacture of mixed diesters

Into a solution of 5.30 mmol phenolic monoester of general formula A in 40 ml dichloromethane under agitation at 0°C a solution of acid chloride (5.83 mmol) in 15 ml dichloromethane is dropped. Then triethylamine-dichloromethane (0.589g/ 5.82 mmol-15 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 50 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following example is manufactured using this method:

R' = $CH(CH_3)_2$

R'' = CH_3

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Colourless oil.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

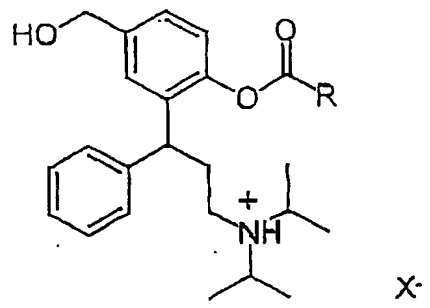
Hydrochloride: colourless crystals

^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$ = +14.6 (c = 1, $CHCl_3$).

CLAIMS

1. Compounds of general formula I



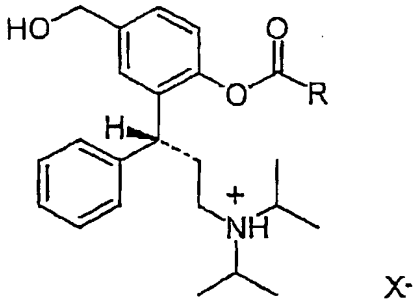
Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

2. Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid,

hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

3. Compounds in accordance with claims 1 and 2, characterised in that they have general formula 2.



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

4 Compounds in accordance with claim 3, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-

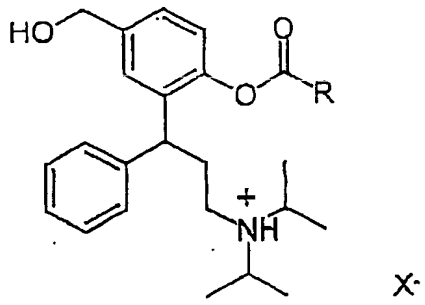
tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

5. Compounds in accordance with claims 3 and 4, characterised in that they are *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate, *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate

6. Compounds in accordance with claims 3 and 4, characterised in that R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

7. Compounds in accordance with claims 1 to 6 in the form of a bulk material.

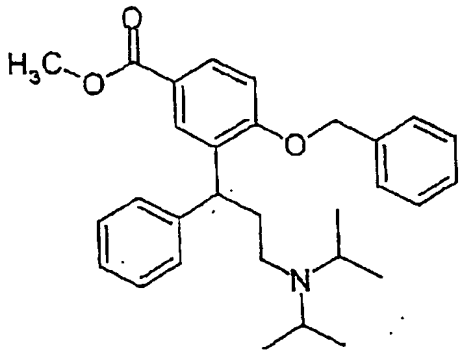
8. Method for manufacturing compounds of general formula I



Formula I

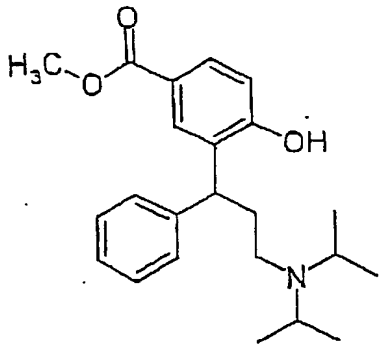
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of formula III



Formula III

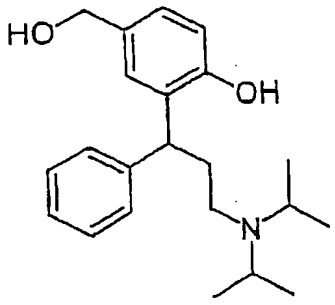
is split with a hydrogenation agent to form a compound of Formula V



Formula V

whereupon

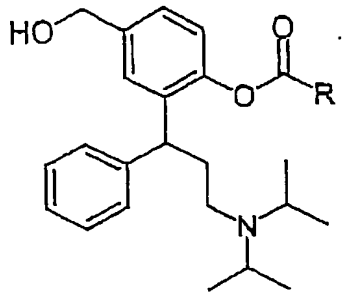
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

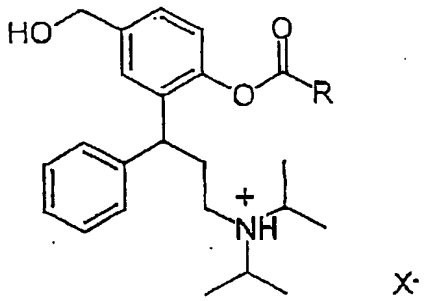
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

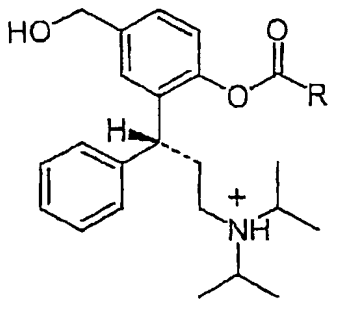


Formula I

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

9. Method in accordance with claim 8, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

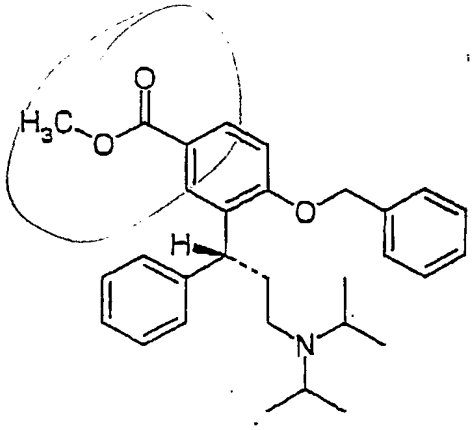
10. Method for manufacturing compounds of general formula 2



Formula 2

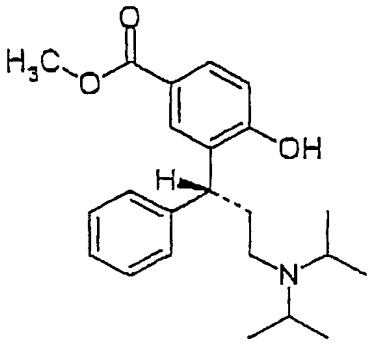
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of the formula 3



Formula 3

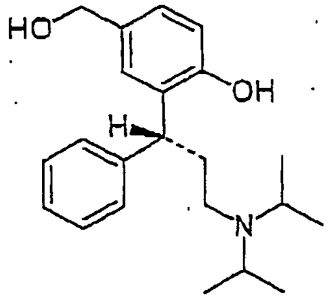
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

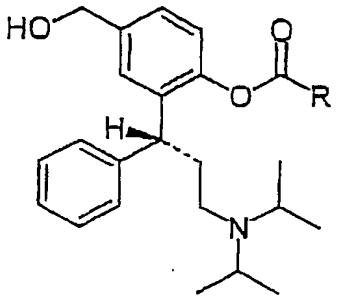
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

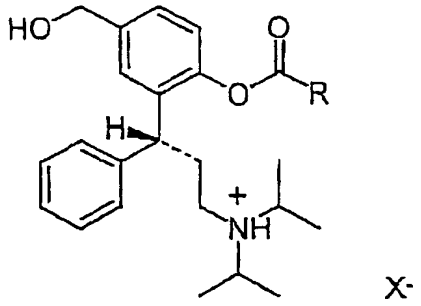
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

11. Method in accordance with claim 10, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-

hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

12. Method in accordance with claims 8 to 11, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

13. Method in accordance with claims 8 to 11, characterised in that for the reducing agent $NaBH_4$/EtOH, preferably $LiAlH_4$/THF, is used.

14. Method in accordance with claims 8 to 11, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

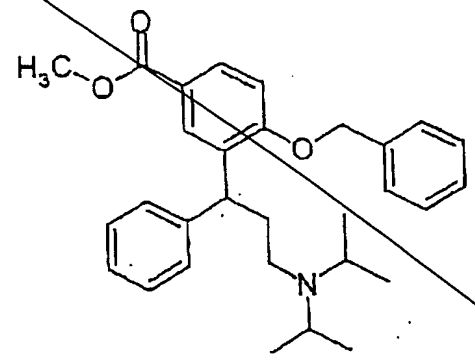
15. Method in accordance with claims 10 to 14, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate.

16. Method in accordance with claims 10 to 15, characterised in that *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid or

hydrochloric acid are converted with the formation of the respective salt.

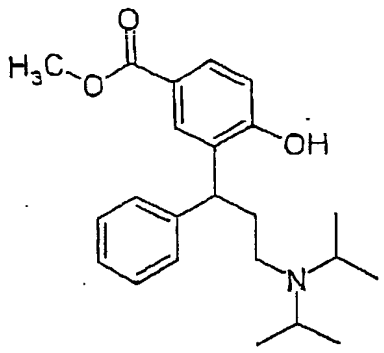
17. Method in accordance with claims 10 to 13 for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of isobutyrate chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

18. Compound of formula III



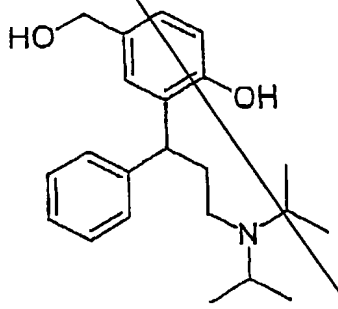
Formula III

19. Compound of formula V



Formula V

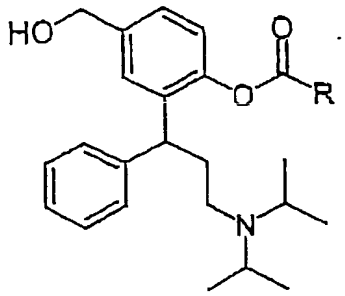
20. Compound of formula VI



Formula VI

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

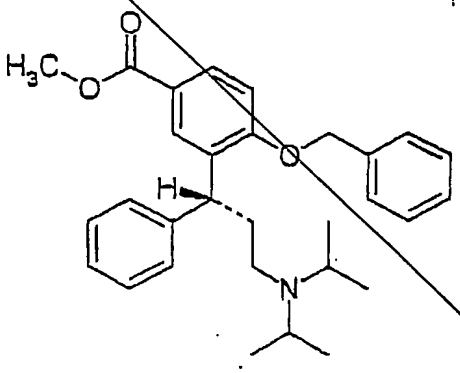
22. Use of a compound in accordance with claims 18 to 20 as an intermediate product in the manufacture of phenolic monoesters of general formula A



Formula A

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl.

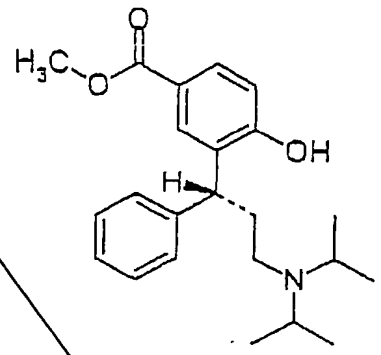
23. Compound of formula 3



Formula 3

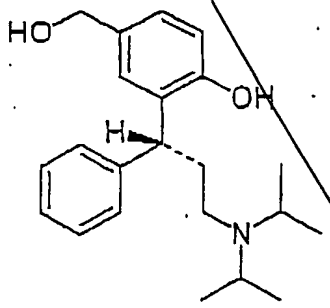
24. Compound of formula 5

A3 cont



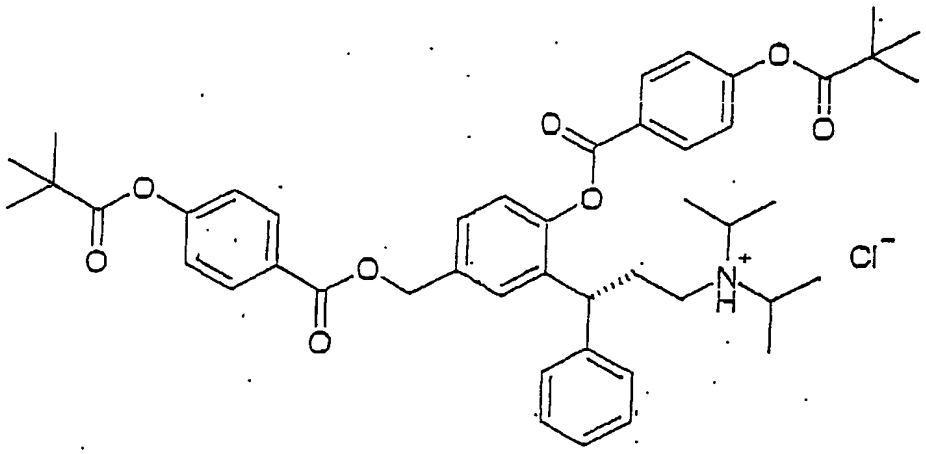
Formula 5

25. Compound of formula 6



Formula 6

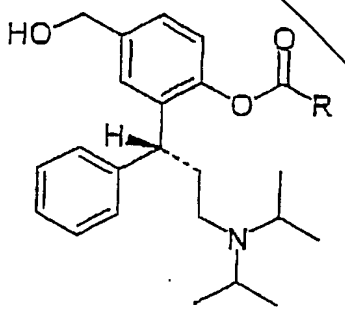
26. Compound of formula 7



Formula 7

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

29. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of salts of phenolic monoesters of general formula 2, in which R has the same meaning as given in claim 3.

30. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

ABSTRACT

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the manufacture and highly pure, stable intermediate products.

The method is in particular characterised by regio- and chemoselectivity and high yield. Salts of phenolic monoesters of 3,3-diphenylpropylamines are provided, that are particularly well-suited for use in pharmaceutical formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate. Furthermore, stable, crystalline intermediate products that are essential for obtaining the abovementioned salts are provided. A preferred intermediate product is *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

	Express Mail N .	
DECLARATION FOR UTILITY, DESIGN, DIVISIONAL AND CONTINUATION-IN-PART PATENT APPLICATIONS (37 CFR 1.63)	Att rney Docket Number	41946/32854
	First Named Invent r	MEESE, Claus
☒ Declaration Submitted with Initial Filing	*COMPLETE IF KNOWN*	
	Application Number	To be assigned
☐ Supplemental Declaration Submitted ☐ Declaration Submitted for Continuation-In-Part Filing ☐ Declaration Submitted for Divisional Filing	Filing Date	To be assigned
	Group Art Unit	To be assigned
	Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-PHENYLPROPYLAMINES

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 11/15/2000 as United States Application Number or PCT International Application Number PCT/EP00/11309 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for pat nt, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
DE 199 55 190.1	Germany	11/16/1999	☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

[redacted] 130214
[redacted]13 Rec'd PCT/PTO 14 MAY 2002

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: SCHWARZ PHARMA AG

Application No./Patent No.:_____ Filed/Issue Date:_____

Entitled: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

SCHWARZ PHARMA AG, a CORPORATION,
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

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The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

2 May 2002
Date

ppa. K.-D. Hommerich i.V. D.W. Schacht
Typed or printed name

Signature

Authorized Officer Assistant Manager
Title

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First Named Inventor	MEESE, Claus
Title	STABLE SALTS OF et al.
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Examiner Name	
Attorney Docket Number	41946/32854

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☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	ppa. K.-D. Hommerich i.V. D. W. Schacht
Signature	
Date	2 May 2002

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ☒ Customer Number or Bar Code Label 021888 OR ☐ Correspondence address below

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Country USA **Telephone** 314-552-6443 **Fax** 314-552-7443

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NAME OF SOLE OR FIRST INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Claus **Family Name or Surname** MEESE

Inventor's Signature Dr. Claus D. Meese **Date** 2 May 2002

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NAME OF SECOND INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) **Family Name or Surname**

Inventor's Signature **Date**

Residence: City **State** **Country** **Citizenship**

Mailing Address

City **State** **ZIP** **Country**

☐ Additional inventors are being named on the ____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

1887648

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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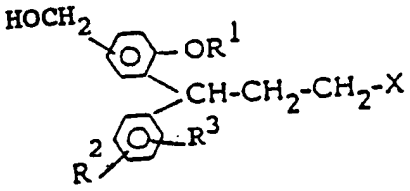
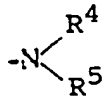
(81) Designated States: AU, CA, FI, HU, JP, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL 3,3-DIPHENYLPROPYLAMINES, THEIR USE AND PREPARATION



(I)



(II)

(57) Abstract

The invention relates to 3,3-diphenylpropylamines of formula (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), 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, and wherein R^4 and R^5 may form a ring together with 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. The invention also relates to methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

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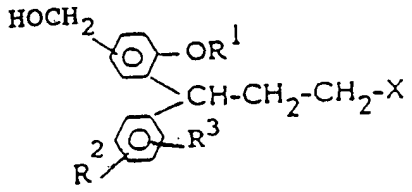
NOVEL 3,3-DIPHENYLPROPYLAMINES, THEIR USE AND PREPARATION

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.

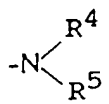
WO 89/06644 discloses 3,3-diphenylpropylamines having anticholinergic activity. In accordance with the present invention novel therapeutically active compounds have now been found, some of which are formed as metabolites in mammals when treated with the 3,3-diphenylpropylamines disclosed in the above-mentioned 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 preferably 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.

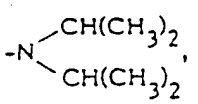
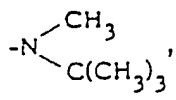
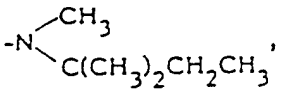
R^2 is preferably in 3-, 4- or 5-position.

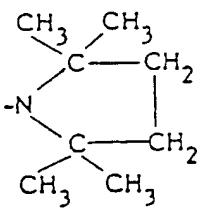
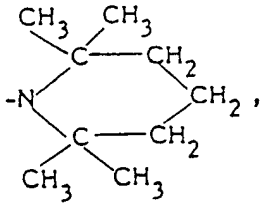
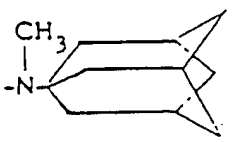
R^3 is preferably in 2-position with respect to the propylamine group.

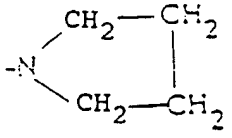
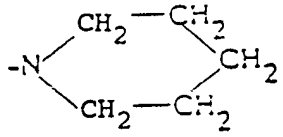
The $HOCH_2$-group is preferably in 5-position.

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) 

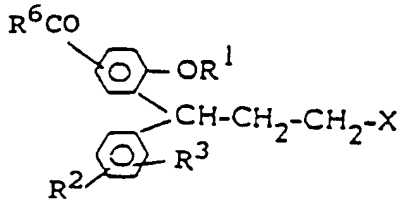
g)  , h) 

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

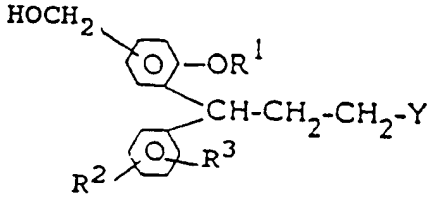
a) reducing the group R^6CO in a 3,3-diphenylpropylamine of formula III



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

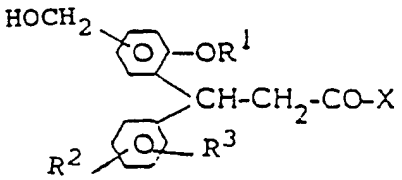
wherein R^1 to R^3 are as defined above and any hydroxy

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

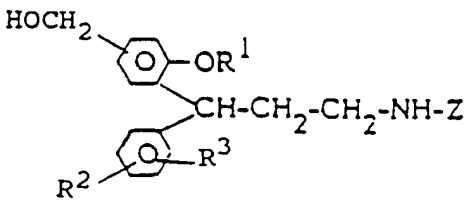
c) reducing a 3,3-diphenylpropionamide of formula VI



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

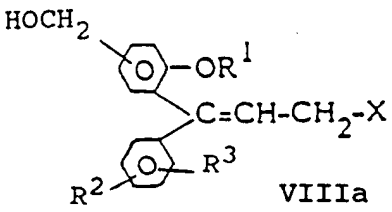
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



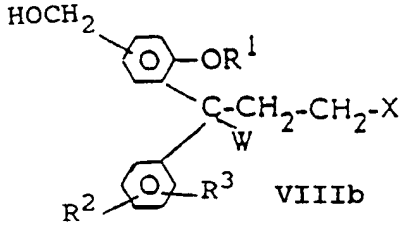
VII

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



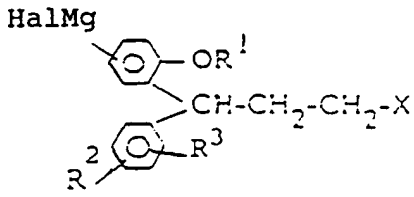
VIIIa



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,

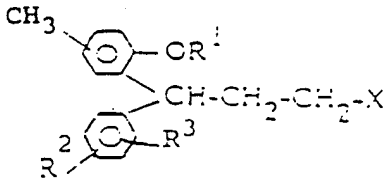
f) reacting a 3,3-diphenylpropylamine of formula IX



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 Tropicalis).

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-hydroxymethylphenyl)-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-phenyl-propanonate

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) <u>(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine hydrochloride</u>

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-carbomethoxy-phenyl)-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-carbomethoxy-phenyl)-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-hydroxymethyl-phenyl)-3-phenylpropylamine

METHOD

(+)-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-hydroxymethyl-phenyl)-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-hydroxymethyl-phenyl)-3-phenylpropylammonium (+) mandelate

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethyl-phenyl)-3-phenylpropylamine (28.2 g, 0.065 mole) was dissolved in methanol (300 g). Raney Nickel (one tea-spoon) 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-hydroxymethyl-phenyl)-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-^{3}H]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.

$K_B = [A]/r-1$ (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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gland and those in the urinary bladder and ileum. Acta Pharmacol. et Toxicol. 1983 b, 53, 304-313.

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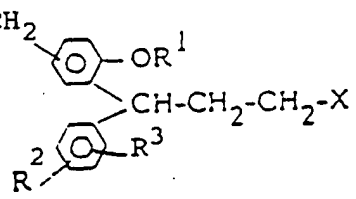
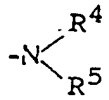
CLAIMS

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



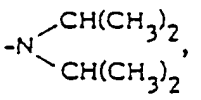
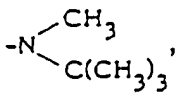
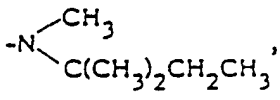
II

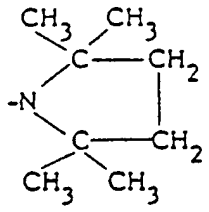
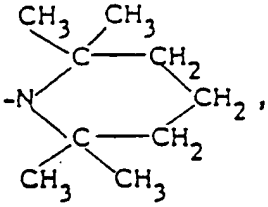
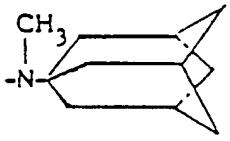
wherein R^4 and R^5 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^4 and R^5 may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

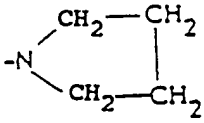
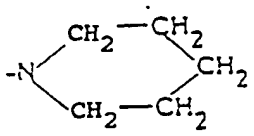
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^4 and R^5 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably 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.

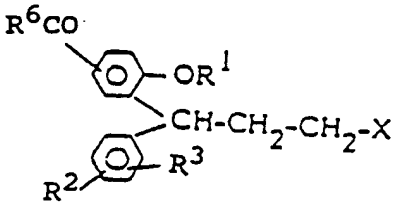
6. 3,3-Diphenylpropylamines according to claim 1, selected from N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine, its salts with physiologically acceptable acids, racemates and individual enantiomers thereof.

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.

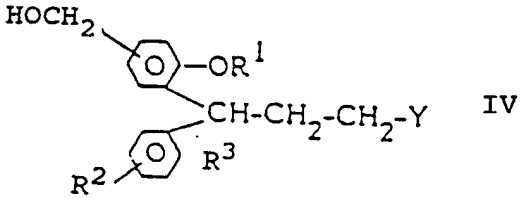
9. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 6 for preparing an anticholinergic drug.

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



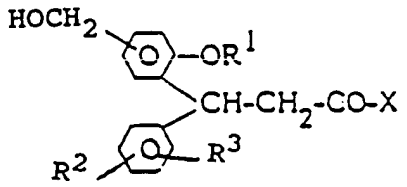
IV

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

$$H - X \qquad V$$

wherein X is as defined above, or

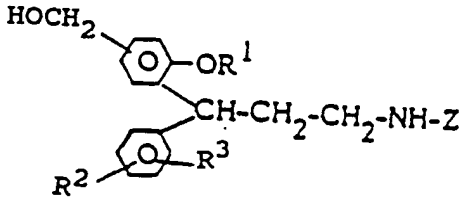
c) reducing a 3,3-diphenylpropionamide of formula VI



VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, or

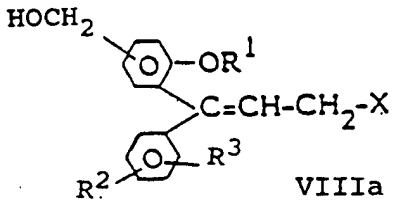
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



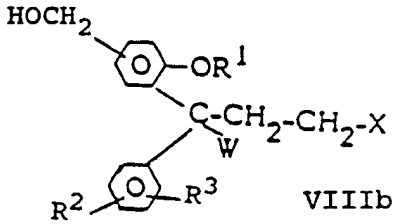
VII

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



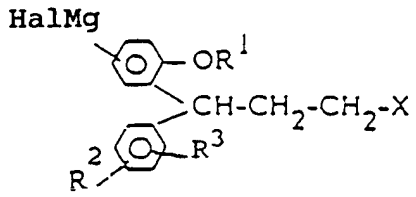
VIIIa



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

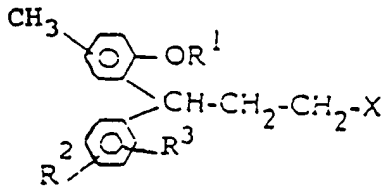
f) reacting a diphenylpropylamine of formula IX



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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00927

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07C 217/62, C07C 215/54, C07C 311/37, C07C 237/30, C07D 295/06, C07D 211/14, C07D 207/06, A61K 31/135
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)

IPC5: C07C, C07D, 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)

CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 8906644 (KABIVITRUM AB), 27 July 1989 (27.07.89) --	1-10
X	DE, B1, 1216318 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING), 12 May 1966 (12.05.66), column 4, line 1 - line 3; t he claims --	1-10
X	GB, A, 1169944 (ED. GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 12; the claims --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00927

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB, A, 1169945 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 11; the claims -- --------	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00927

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1 in part
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:
The wording "R^4 and R^5 may form a ring together with the amine nitrogen" is too broadly formulated to permit a meaningful search. The search on claim 1 has therefore been incomplete (See Art. 6).

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

27/11/93

International application No.
PCT/SE 93/00927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 8906644	27/07/89	AU-B- 635493	25/03/93
		AU-A- 2932989	11/08/89
		DE-U- 6890018	12/09/91
		EP-A,B- 0325571	26/07/89
		SE-T3- 0325571	
DE-B1- 1216318	12/05/66	DK-A- 111894	00/00/00
GB-A- 1169944	05/11/69	NONE	
GB-A- 1169945	05/11/69	US-A- 3446901	27/05/69

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(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

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(72) Inventors; and

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(74) Agents: WIDÉN, Björn et al.; Pharmacia & Upjohn AB, Patent Dept., S-751 82 Uppsala (SE).

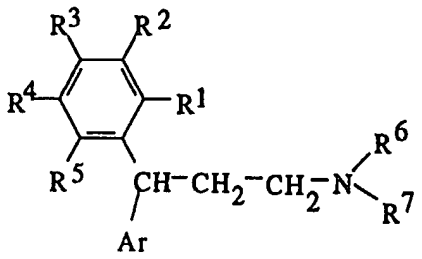
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, 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).



(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.

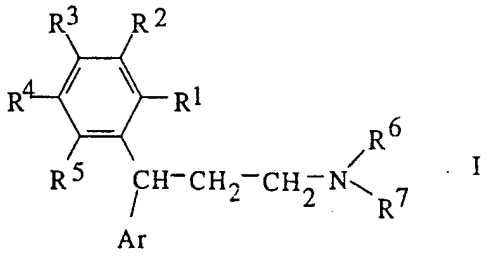
BACKGROUND OF THE INVENTION

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.

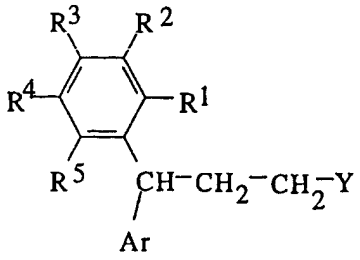
Exemplary groups $-NR^6,R^7$ are diethylamino, diisopropylamino, methyl-tert.-butylamino, methyl-tert.-pentylamino, piperidino, 2,2,6,6-tetramethylpiperidino, methylcyclobutylamino, methylcyclopentylamino, methylcyclohexylamino, methylcycloheptylamino, pyrrolidino, 2,2,5,5-tetramethylpyrrolidino, N-methyl-N-adamantylamino,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

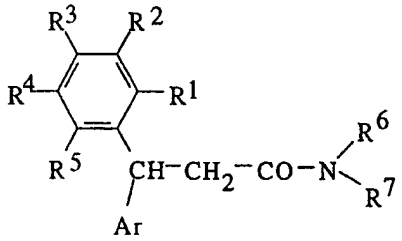
a) reacting a compound of Formula II



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

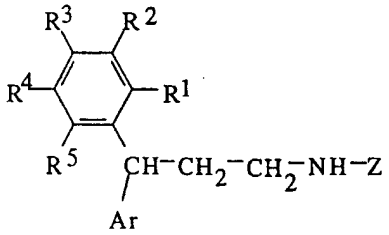
b) reducing a compound of Formula III



III

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

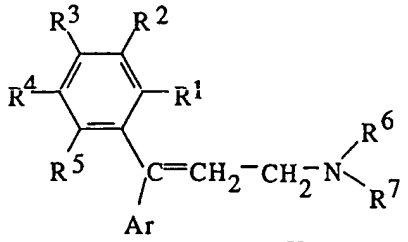
c) N-alkylating a secondary amine of Formula IV



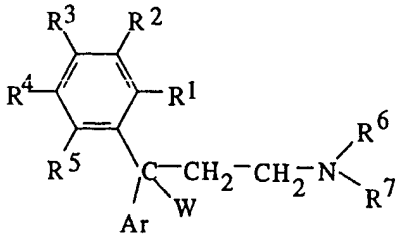
IV

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



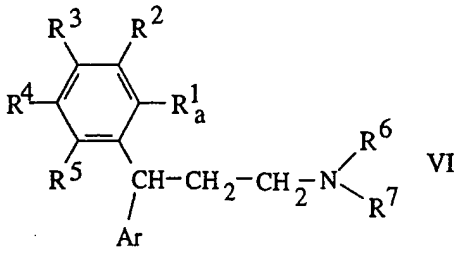
Va



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

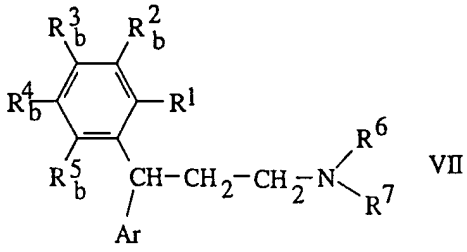
e) in a compound of Formula VI



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

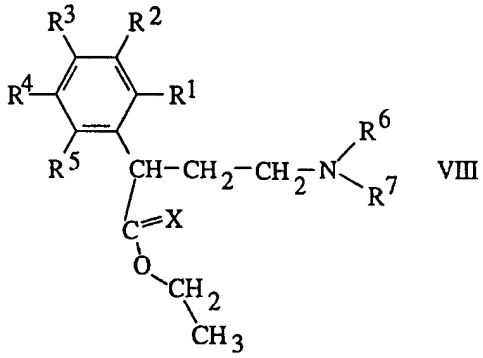


VII

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

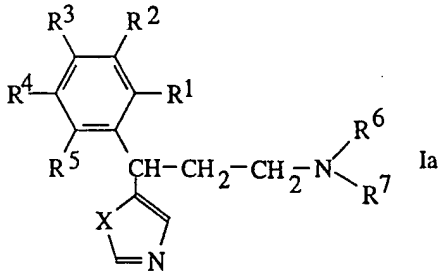


VIII

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

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

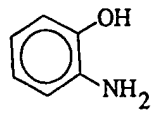
to form a compound of Formula Ia



Ia

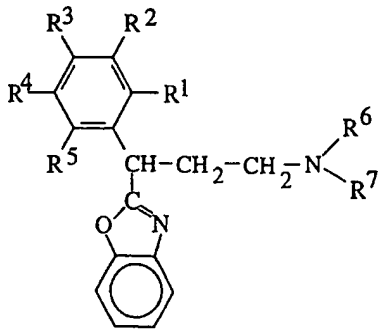
wherein R^1 to R^7 and X are as defined above, or

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



X

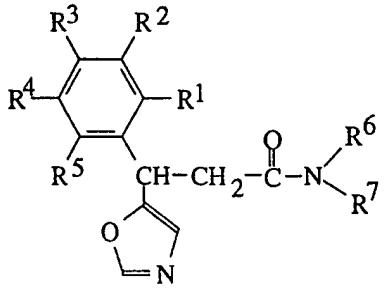
to form a compound of Formula Ib



Ib

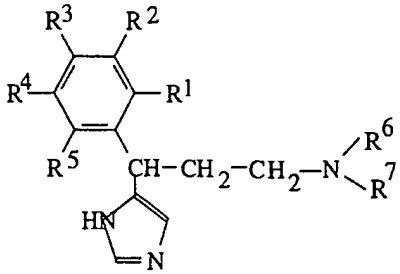
wherein R^1 to R^7 are as defined above for Formula I, or

j) converting a compound of Formula XI



XI

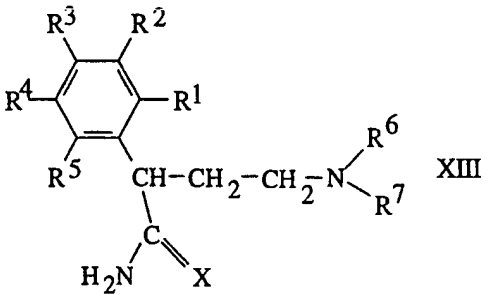
wherein R^1 to R^7 are as defined above for Formula I, to a compound of Formula XII



XII

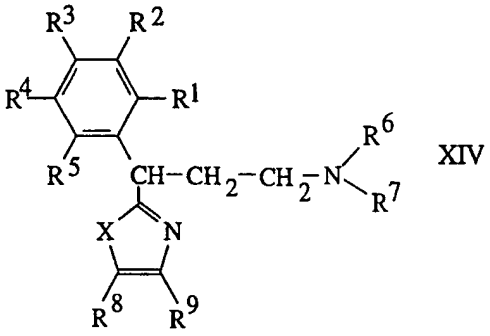
wherein R^1 to R^7 are as defined above for Formula I, or

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

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%); ^1H 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

(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%). ^1H 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

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); ^1H 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.

Preparation of starting compounds:

12.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

Yield 5.5 g (53%); ^1H 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

Yield 1.2 g (75%); ^1H 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

(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); ^1H 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.

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

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%); ^1H 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

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.

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

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

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); ^{1}H 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.

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

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

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.

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

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.

The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine was prepared as follows:

17.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine

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

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

(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

(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.

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-benzyloxy-phenyl)-3-phenylpropanamine

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

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

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethyl-phenyl)-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); ^{1}H 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

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; ^{1}H 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.

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

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

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. ^1H 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

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. ^1H 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

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

(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.

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

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-hydroxy-phenyl]-3-phenylpropanamine hydrochloride

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 %). ^{1}H 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

(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 %); ^{1}H 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-hydroxy-phenyl]-3-phenylpropanamine hydrochloride.

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%); ^{1}H 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

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

(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 %); ^1H 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.

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

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}; ^1H

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

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}; ^1H 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).

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

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

$NaNO_2$ (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. ^1H 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

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

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); ^{1}H 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.

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

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

(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%); ^{1}H 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

(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); ^{1}H 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

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; ^1H 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.

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

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%); ^1H 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

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

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.

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

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

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-phenylpropanamine hydrochloride

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.

The starting compound N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide was prepared as follows:

33.1 2-(3,5-Dimethyl-4-hydroxyphenylazo)benzophenone

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

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%); ^1H 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-tosyloxyphenyl-azo)phenyl]-3-phenylpropenamide

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%). ^1H 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-hydroxyphenyl-azo)phenyl]-3-phenylpropenamide

A solution of potassium hydroxide (10.3 mL, 6 M) and N,N-diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenyl-azo)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

N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenyl-azo)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

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; ^{1}H 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).

The starting compound N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine was prepared as follows:

34.1 N,N-Diisopropyl-3-cyano-3-phenylpropanamine

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-Chloroethyl-diisopropylamine (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. ^{1}H 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

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%); ^{1}H 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

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-phenylpropanamine hydrochloride

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

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%): ^1H 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).

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

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%): ^1H 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

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 ice-bath. 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%): ^1H NMR ($CDCl_3$) 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

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

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

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

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; ^1H 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

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; ^1H 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).

The starting compound N,N-diisopropyl-3-phenyl-3-thiocarbamoylpropanamine was prepared as follows:

38.1 N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine

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%): ^1H 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-phenyl-propanamine hydrochloride

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

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).

The starting compound N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine was prepared as follows:

40.1 N,N-Diisopropyl-3-ethoxythiocarbonyl-3-phenyl-propanamine

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%): ^1H 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

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; ^1H 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).

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

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%): ^1H 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

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

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%): ^1H 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

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. ^1H 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).

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

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

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

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

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

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

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

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

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

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)propanamine hydrochloride

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

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

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

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

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

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

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).

The starting compound was prepared as follows:

57.1 N,N-Diisopropyl-3-(3-thienyl)propenamide

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

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).

The starting compound was prepared as follows:

58.1 N,N-Diisopropyl-3-(2-furanyl)propenamide

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

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).

The starting compound was prepared as follows:

59.1 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide

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

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

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

The pharmacological activity of compounds prepared in the Examples was tested using in vitro methods.

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 stabilise for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilisation period.

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:

$$K_B = [A]/r-1 \quad (1)$$

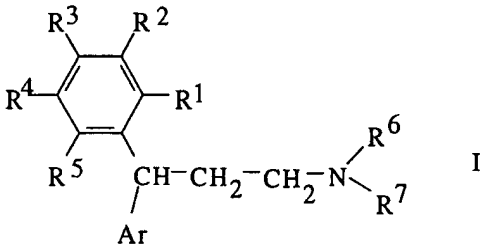
The KB values obtained are presented in Table 1 below.

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
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, alkoxycarbonyl, 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, aminoalkyl, 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 hydroxyethoxyethyl-aminoethyl.

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-methyloxycarbonyl-phenyl)-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.

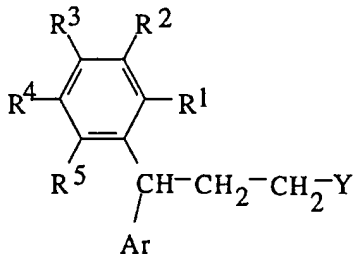
21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19, and preferably a compatible pharmaceutical carrier.

22. Use of a compound according to any one of claims 1 to 19 for preparing an anticholinergic drug.

23. A method of treating a living body suffering from a disorder related to urinary incontinence, which method comprises the step of administering to said living body an effective amount of a compound according to any one of claims 1 to 19.

24. A method of preparing a compound according to any one of claims 1 to 19, which comprises:

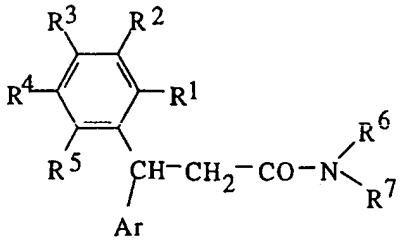
a) reacting a compound of Formula II



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

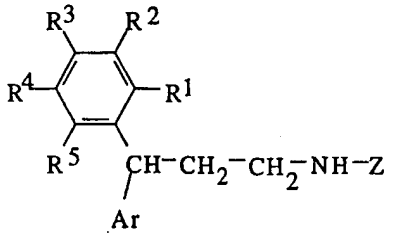
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, or

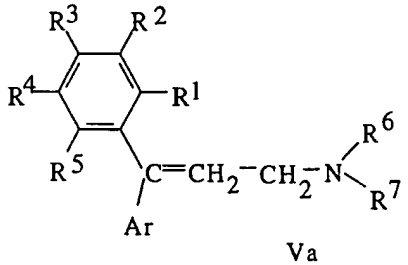
c) N-alkylating a secondary amine of Formula IV



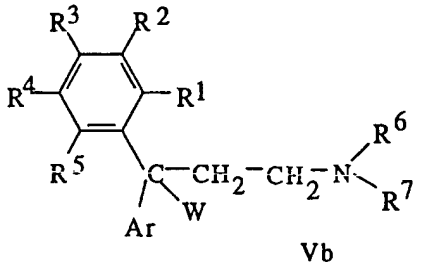
IV

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



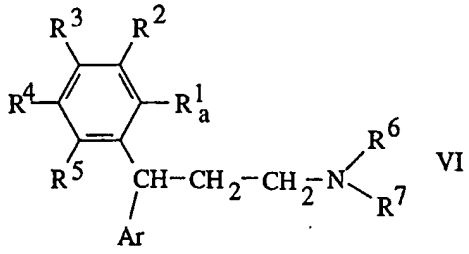
Va



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

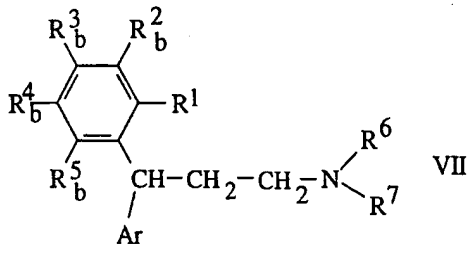
e) in a compound of Formula VI



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

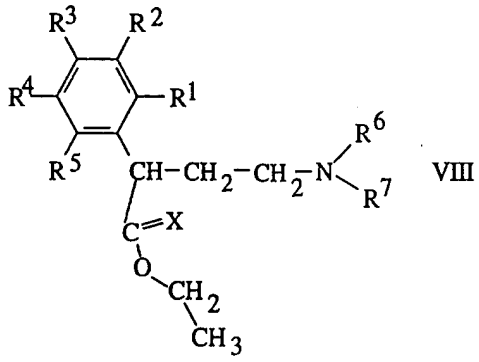


VII

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

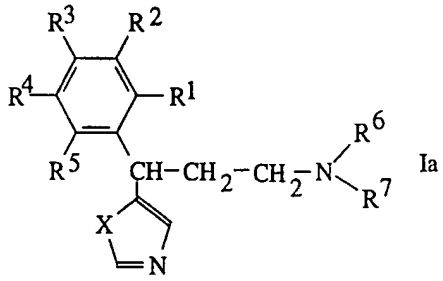


VIII

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

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

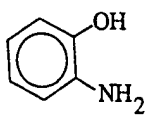
to form a compound of Formula Ia



Ia

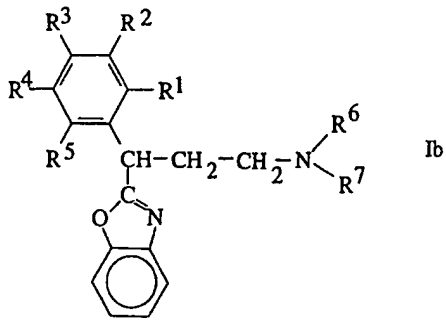
wherein R^1 to R^7 and X are as defined above, or

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



X

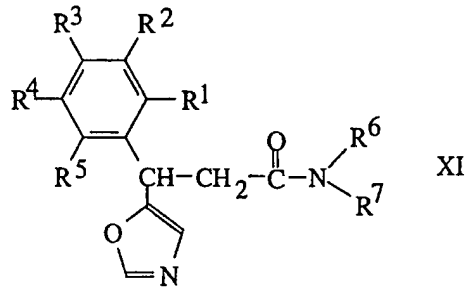
to form a compound of Formula Ib



Ib

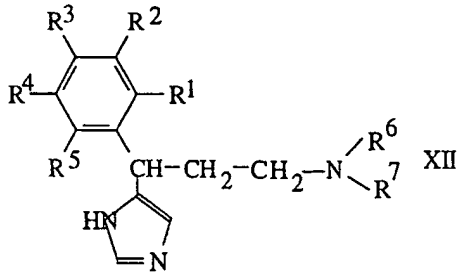
wherein R^1 to R^7 are as defined in claim 1, or

j) converting a compound of Formula XI



XI

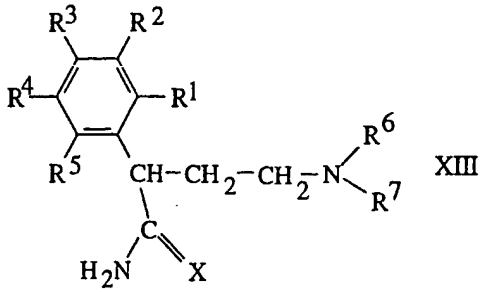
wherein R^1 to R^7 are as defined in claim 1, to a compound of Formula XII



XII

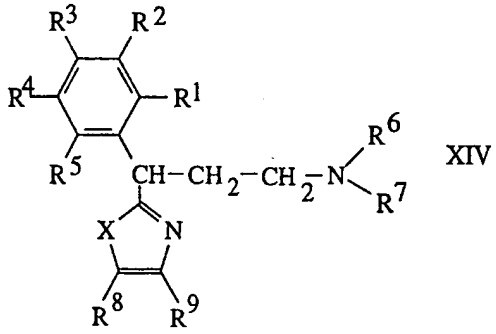
wherein R^1 to R^7 are as defined in claim 1, or

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 211/06, C07C 215/54, C07C 217/62, C07C 237/30, C07C 255/33, C07D 333/20, A61K 31/135, A61K 31/33

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: C07C, C07D, 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)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9411337 A1 (KABI PHARMACIA AB), 26 May 1994 (26.05.94) --	1-22,24
X	WO 8906644 A1 (KABIVITRUM AB), 27 July 1989 (27.07.89) --	1-22,24
X	DE 1216318 B1 (FARBWERKE HOECHST AKTIENGESELLSCHAFT VORMALS MEISTER LUCIUS & BRüNING), 12 May 1966 (12.05.66), column 4, line 1 - line 4, the claims --	1-21,24

[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

"E" erlier document but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1998	29 -06- 1998
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 Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1169944 A (ED. GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 12, the claims ---	1-21,24
X	GB 1169945 A (ED GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 11, the claims --- --------	1-21,24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

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.: 23
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

09/06/98

International application No.
PCT/SE 98/00556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411337 A1	26/05/94	AT 164828 T	15/04/98
		AU 672458 B	03/10/96
		AU 5438094 A	08/06/94
		CA 2148827 A	26/05/94
		DE 69317898 D	00/00/00
		EP 0667852 A,B	23/08/95
		FI 952179 A	05/05/95
		HU 72742 A	28/05/96
		HU 9501329 D	00/00/00
		JP 8503208 T	09/04/96
		NO 951775 A	05/05/95
		SE 9203318 D	00/00/00
		US 5559269 A	24/09/96
		US 5686464 A	11/11/97
WO 8906644 A1	27/07/89	AU 635493 B	25/03/93
		AU 2932989 A	11/08/89
		DE 6890018 U	12/09/91
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		DK 172590 A	19/07/90
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		EP 0325571 A,B	26/07/89
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		EP 0354234 A	14/02/90
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		HU 9400053 A	30/01/95
		JP 2664503 B	15/10/97
		JP 3503163 T	18/07/91
		NO 173496 C	22/12/93
		SE 8800207 D	00/00/00
		US 5382600 A	17/01/95
DE 1216318 B1	12/05/66	DK 111894 A	00/00/00
GB 1169944 A	05/11/69	NONE	
GB 1169945 A	05/11/69	US 3446901 A	27/05/69

10/130214

PTO/SB/42 (08-00) #3

Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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JC13 Rec'd PCT/PTO 14 MAY 2002

Sheet 1 of 1

37 CFR 1.501 INFORMATION DISCLOSURE CITATION IN A PATENT (Use several sheets if necessary)	Docket Number (Optional) 41946/32854	Application Number New
	Applicant Claus Meese et al.	
	Filing Date Herewith	Group Art Unit to be assigned

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES	TRANSLATION NO
	BA	EP 0 667 852 B1	4/8/98	EPO	C07C 217	62	x	
	BB	DE 693 17 898 T2	10/15/98	Germany	C07C 217	62	x	
	BC	EP 0 957 073 A1	11/17/99	EPO	C07C1	00	x	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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BA

(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

(73) Proprietor: **Pharmacia & Upjohn Aktiebolag**
112 87 Stockholm (SE)

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- **NILVERBANT, Lisbeth**
  S-161 35 Bromma (SE)
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  S-142 65 Trangsund (SE)

(74) Representative: **Widén, Björn et al**
Pharmacia & Upjohn AB,
Patent Department
751 82 Uppsala (SE)

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

EP 0 667 852 B1

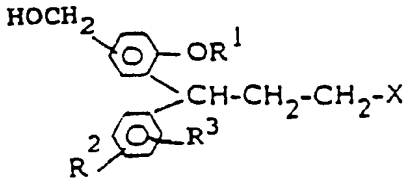
Printed by Jouve, 75001 PARIS (FR)

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.

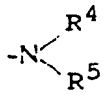
WO 89/06644 discloses 3,3-diphenylpropylamines having anticholinergic activity. In accordance with the present invention novel therapeutically active compounds have now been found, some of which are formed as metabolites in mammals when treated with the 3,3-diphenylpropylamines disclosed in the above-mentioned 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.

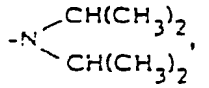
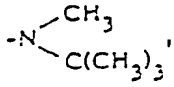
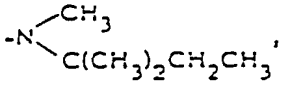
R^2 is preferably in 3-, 4- or 5-position.

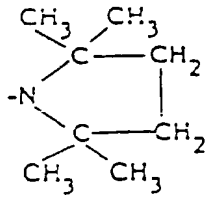
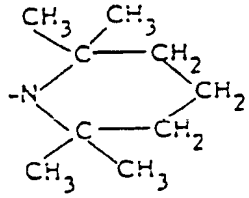
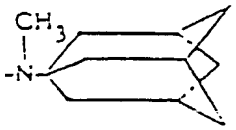
R^3 is preferably in 2-position with respect to the propylamine group.

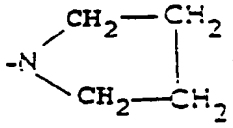
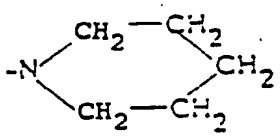
The $HOCH_2$-group is preferably in 5-position.

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) 

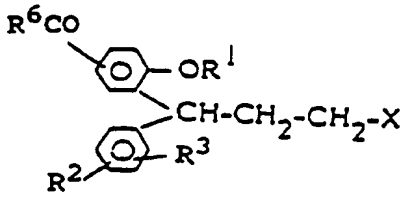
g)  , h) 

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

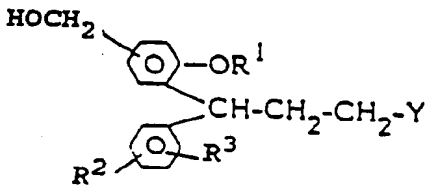
a) reducing the group R^6CO in a 3,3-diphenylpropylamine of formula III



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



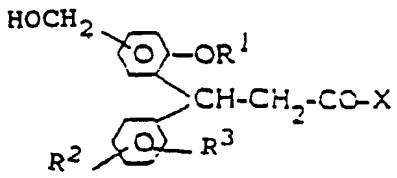
IV

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

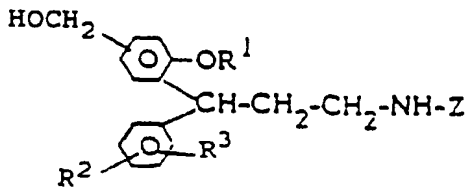
wherein X is as defined above, or

c) reducing a 3,3-diphenylpropionamide of formula VI



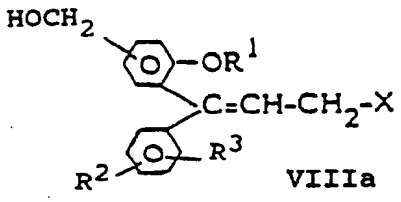
VI

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

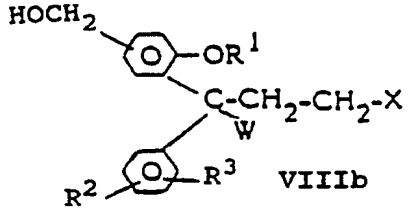


VII

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

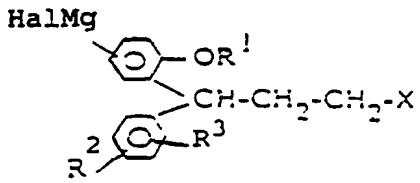


VIIIa



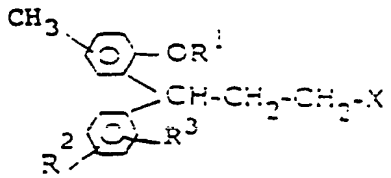
VIIIb

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-hydroxymethylphenyl)-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 th oretical 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 w re 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.

$$K_B = [A]/r-1 \quad (1)$$

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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2. Nilvebrant, L.; Sparf, B. Muscarinic receptor binding in the guinea pig urinary bladder. Acta Pharmacol. et Toxicol. 1983 a, 52, 30-38.
3. Nilvebrant, L; Sparf, B. Dicyclomine, benzhexol and oxybutynin distinguish between sub-classes of muscarinic binding-sites. Eur. J. Pharmacol. 1986, 123, 133-143.
4. D Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. Protein measurement with the Folin phenol reagent. J. Biol. Chem. 1951, 193, 265-275.
5. Nilvebrant, L.; Sparf, B. Differences between binding affinities of some antimuscarinic drugs in the parotid gland and those in the urinary bladder and ileum. Acta Pharmacol. et Toxicol. 1983 b, 53, 304-313.
6. Jacobs, S.; Chang, K.-J.; Cuatrecasas, P. Estimation of hormone receptor affinity by competitive displacement of labelled ligand. Effects of concentration of receptor and labelled ligand. Biochem. Biophys. Res. Commun. 1975, 66, 687-692.
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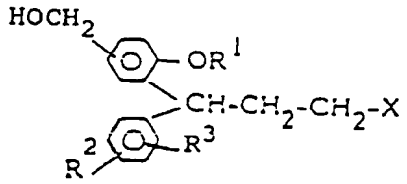
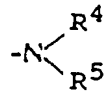
Claims

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



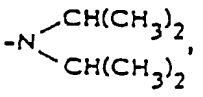
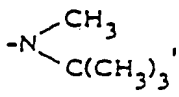
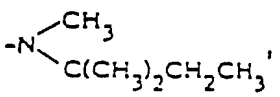
II

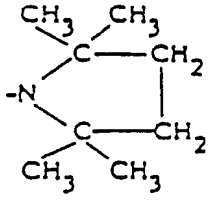
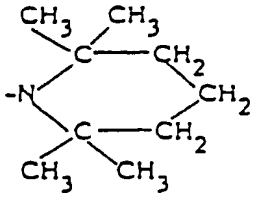
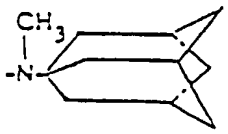
wherein each of R^4 and R^5 independently signify non-aromatic hydrocarbyl groups, which may carry one or more hydroxy groups and which together contain at least three carbon atoms, and wherein R^4 and R^5 may be joined to form a ring having no other heteroatom than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

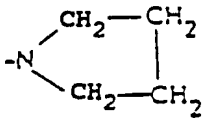
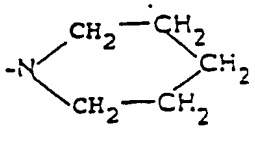
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^4 and R^5 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably 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.

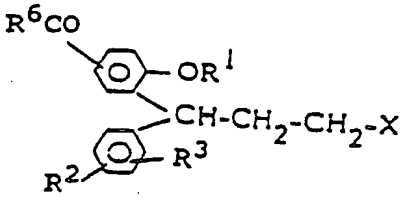
7. 3,3-Diphenylpropylamines according to any one of claims 1 to 6 for use as pharmaceutically active substances, especially as anticholinergic agents.

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.

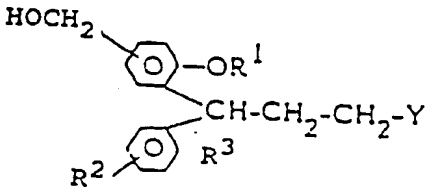
10. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1 to 6, comprising:

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

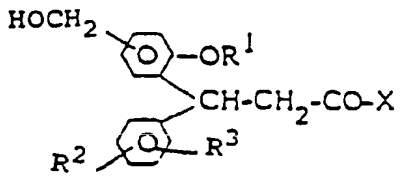


IV

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

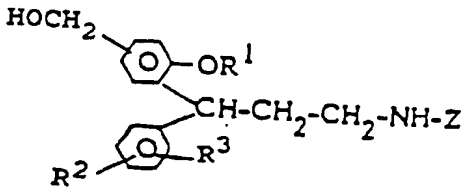
H - X V

wherein X is as defined above, or
c) reducing a 3,3-diphenylpropionamide of formula VI



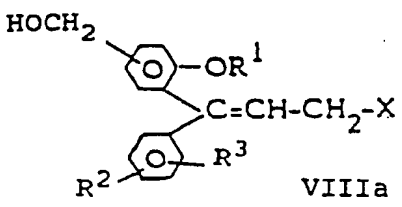
VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, or
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII

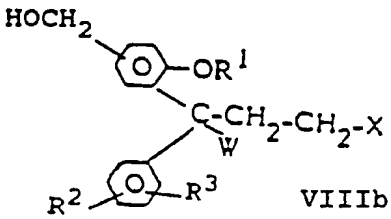


VII

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

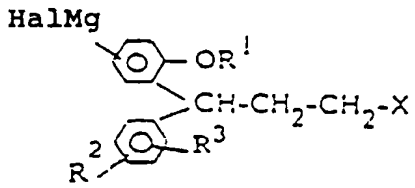


VIIIa



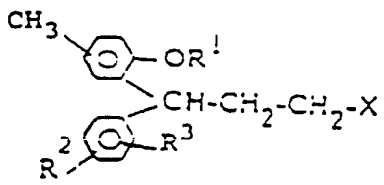
VIIIb

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



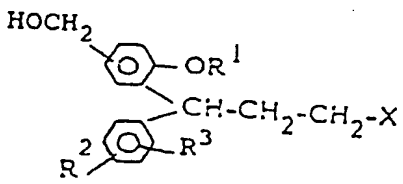
X

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.

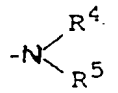
Patentansprüche

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



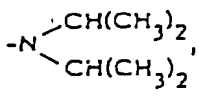
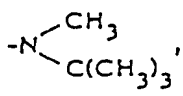
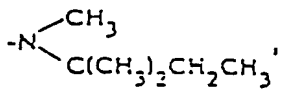
II

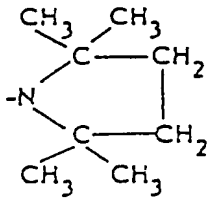
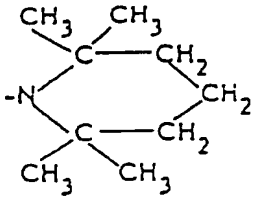
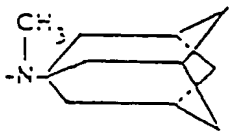
steht, in der jedes R^4 und R^5 unabhängig voneinander für nichtaromatische Kohlenwasserstoffgruppen steht, die eine oder mehrere Hydroxygruppen tragen können und die zusammen wenigstens drei Kohlenstoffatome enthalten und in der R^4 und R^5 miteinander verbunden sein können, um einen Ring zu bilden, 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.

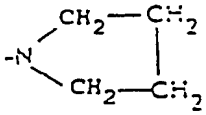
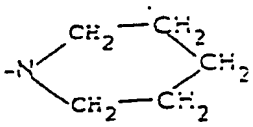
2. 3,3-Diphenylpropylamine nach Anspruch 1, dadurch **gekennzeichnet**, daß jedes R^4 und R^5 unabhängig voneinander eine gesättigte Kohlenwasserstoffgruppe, insbesondere eine gesättigte aliphatische Kohlenwasserstoffgruppe, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl bedeutet und R^4 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.

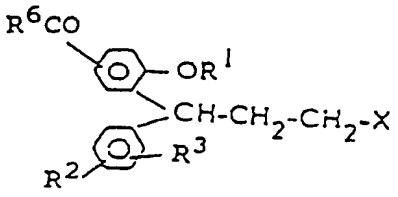
7. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 6 zur Verwendung als pharmazeutisch aktive Substanzen, insbesondere als anticholinerge Mittel.

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:

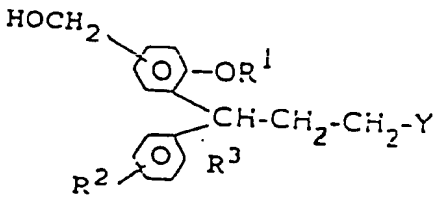
a) Reduktion der R^6CO-Gruppe eines 3,3-Diphenylpropylamins der Formel III



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

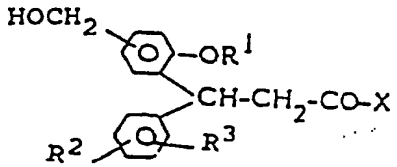


IV

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

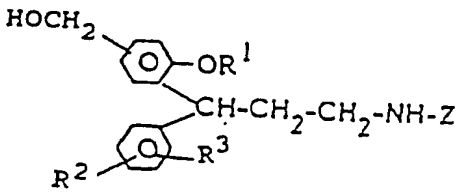
$$H-X \qquad V,$$

in der X die oben definierte Bedeutung hat oder
c) Reduktion eines 3,3-Diphenylpropionamids der Formel VI



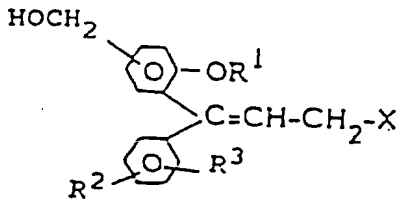
VI

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

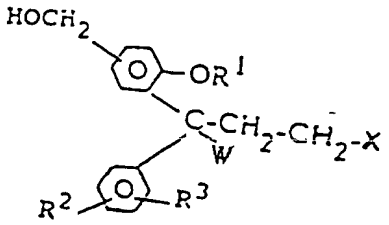


VII

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



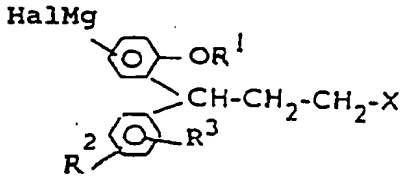
VIIIa



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

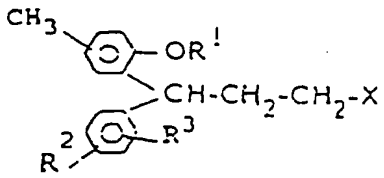
f) Umsetzung eines Diphenylpropylamins der Formel IX



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

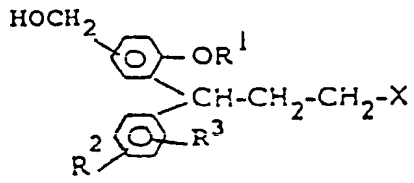
ii) falls gewünscht, Umwandlung der erhaltenen Basen der Formel I in die Salze davon mit physiologisch annehmbaren Säuren oder umgekehrt, und/oder

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.

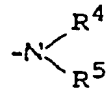
Revendications

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



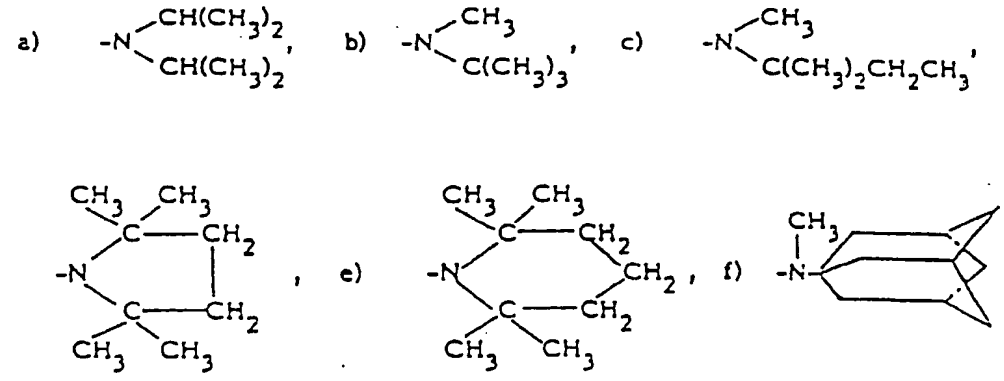
II

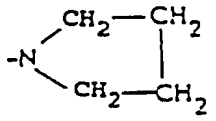
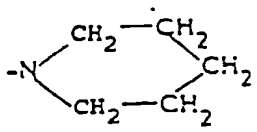
dans laquelle chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle non aromatique, qui peut porter un ou plusieurs groupes hydroxy, les groupes R^4 et R^5, conjointement, contenant au moins trois atomes de carbone, et dans laquelle R^4 et R^5 peuvent être joints en formant un 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.

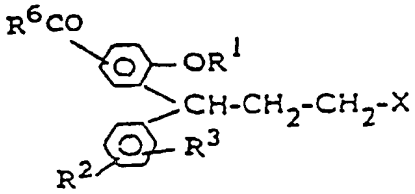
7. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, destinées à être utilisées comme substances pharmaceutiquement actives, notamment comme agents anticholinergiques.

8. Composition pharmaceutique comprenant une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 et, de préférence, un support pharmaceutiquement compatible.

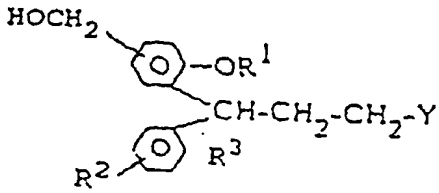
9. Utilisation d'une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 pour la préparation d'un médicament anticholinergique.

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

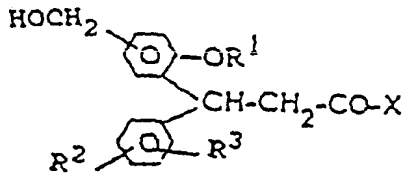
dans laquelle R^1 à R^3 et X répondent aux définitions précitées, R^6 représente l'hydrogène ou un groupe R^7O, dans lequel R^7 représente l'hydrogène, un groupe alkyle, alcényle, alcynyle ou aryle, et n'importe quels groupes hydroxy peuvent être protégés, par exemple par méthylation ou benzylation, 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

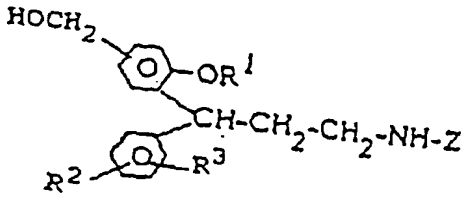
H - X V

dans laquelle X répond à la définition précitée, ou
c) la réduction d'un 3,3-diphénylpropionamide de formule VI



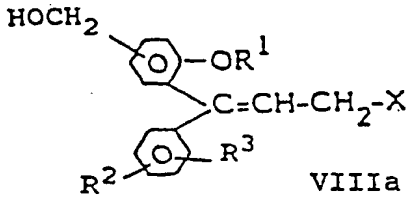
VI

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

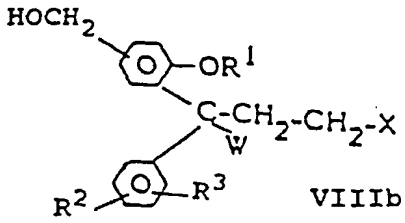


VII

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

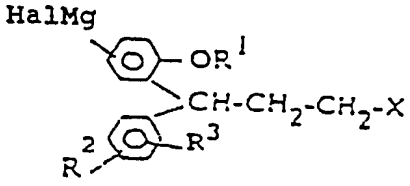


VIIIa



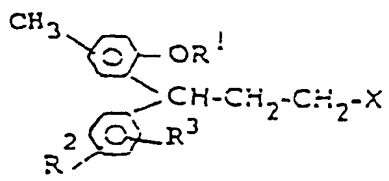
VIIIb

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.

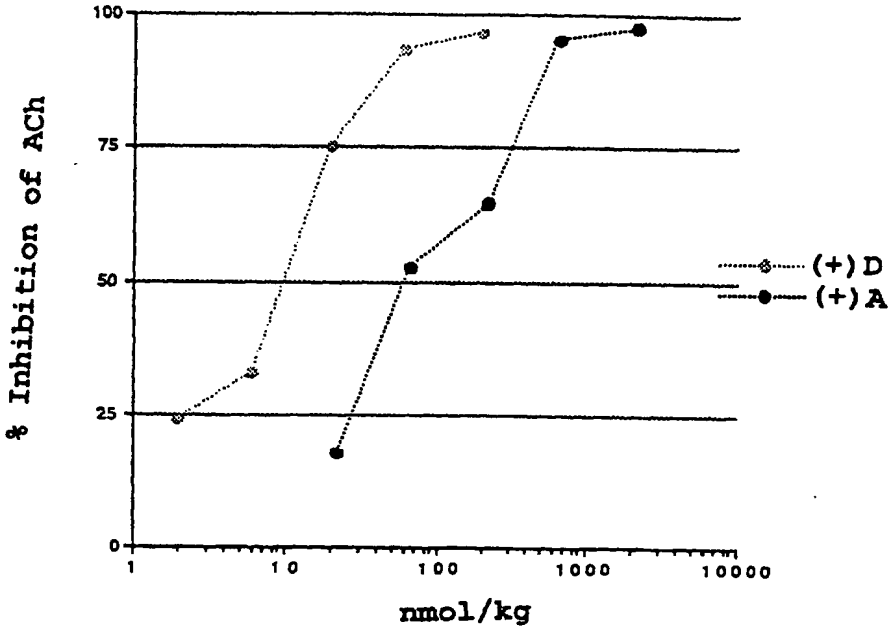


FIG. 1

(19) BUNDESREPUBLIK DEUTSCHLAND

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(11) Übersetzung der europäischen Patentschrift

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C 07 C 237/30
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C 07 D 207/06
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(54) 3,3-DIPHENYLPROPYLAMINE, IHRE VERWENDUNG UND HERSTELLUNG

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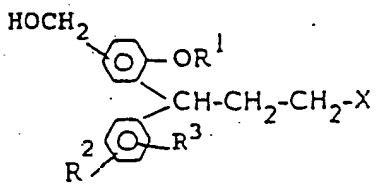
Die Erfindung betrifft neue therapeutisch aktive Verbindungen, Verfahren zu ihrer Herstellung, pharmazeutische Zusammensetzungen, die die neuen Verbindungen enthalten und die Verwendung der Verbindungen zur Herstellung von Arzneimitteln.

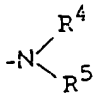
WO 89/06644 beschreibt 3,3-Diphenylpropylamine, die anticholinerge Aktivität besitzen. Erfindungsgemäß wurden nun neue therapeutisch aktive Verbindungen gefunden, von denen einige als Metaboliten in Säugetieren gebildet werden, wenn diese mit den 3,3-Diphenylpropylaminen, die in der oben erwähnten WO-Publikation beschrieben wurden, behandelt werden. Diese Metaboliten haben wenigstens genauso günstige anticholinerge Eigenschaften wie die Ausgangsverbindungen und können somit zur Kontrolle von Ereignissen verwendet werden, die durch Acetylcholin vermittelt werden, wie z.B. das Urinieren.

Die neuen erfindungsgemäßen Verbindungen werden durch die allgemeine Formel I dargestellt



I

worin R^1 Wasserstoff oder Methyl bedeutet, R^2 und R^3 unabhängig Wasserstoff, Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen bedeuten und X eine tertiäre Aminogruppe der Formel II darstellt,



II

in der R^4 und R^5 nichtaromatische Kohlenwasserstoffgruppen bedeuten, die gleich oder verschieden sein können, und die zusammen wenigstens drei Kohlenstoffatome enthalten, vorzugsweise wenigstens vier Kohlenstoffatome, insbesondere wenigstens fünf Kohlenstoffatome, und in der R^4 und R^5 zusammen mit dem Aminstickstoff einen Ring bilden können, wobei der Ring kein anderes Heteroatom besitzt als den Aminstickstoff.

Die Verbindungen der Formel I können Salze mit physiologisch annehmbaren organischen und anorganischen Säuren bilden, und die Erfindung umfaßt die freien Basen ebenso wie die Salze davon. Beispiele für derartige Säureadditionssalze schließen die Salze der Salzsäure, der Bromwasserstoffsäure, der Fumarsäure und dgl. ein.

Liegen die neuen Verbindungen in Form optischer Isomere vor, umfaßt die Erfindung das racemische Gemisch ebenso wie die individuellen Isomere als solche.

In den Verbindungen der Formel I ist R^2 vorzugsweise Wasserstoff und R^3 ist vorzugsweise Wasserstoff oder Hydroxy.

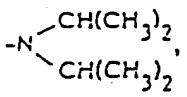
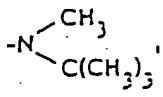
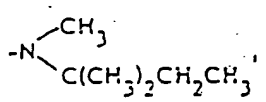
R^2 ist vorzugsweise in der 3-, 4- oder 5-Position.

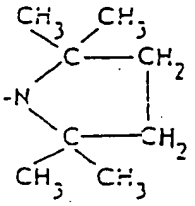
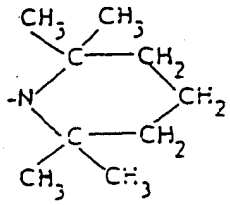
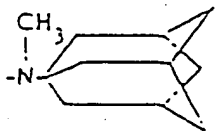
R^3 ist vorzugsweise in der 2-Position in Bezug auf die Propylamingruppe.

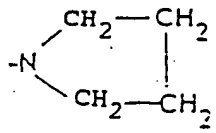
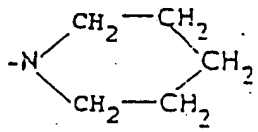
Die $HOCH_2$-Gruppe befindet sich vorzugsweise in der 5-Position.

Vorzugsweise bedeutet jedes R^4 und R^5 unabhängig voneinander C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl, R^4 und R^5 umfassen zusammen wenigstens drei, vorzugsweise wenigstens 4 Kohlenstoffatome. R^4 und R^5 können eine oder mehrere Hydroxygruppen tragen, und sie können miteinander verbunden werden, um zusammen mit dem Aminstickstoffatom einen Ring zu bilden.

Derzeit bevorzugte tertiäre Aminogruppen X in der Formel I schließen die folgenden Gruppen a) - h) ein:

a)  , b)  , c)  ,

d)  , e)  , f) 

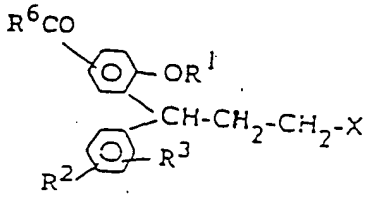
g)  , h) 

Vorzugsweise sind sowohl R^4 als auch R^5 Isopropyl.

Eine derzeit bevorzugte spezifische Verbindung der Formel I ist N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin.

Die Verbindungen der Formel I können erfindungsgemäß durch an sich konventionelle Verfahren hergestellt werden und insbesondere durch

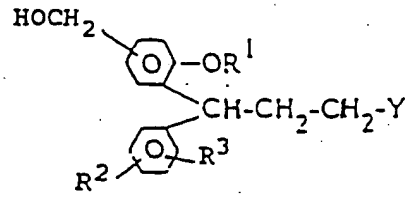
a) Reduktion der R^6CO-Gruppe in einem 3,3-Diphenylpropylamin der Formel III



III

in der R^1 bis R^3 und X die wie oben definierte Bedeutung haben, R^6 Wasserstoff oder R^7O ist, wobei R^7 Wasserstoff, (vorzugsweise niedrig-)Alkyl, Alkenyl, Alkinyl oder Aryl (wie z.B. Phenyl) ist und jegliche Hydroxygruppen z.B. durch Methylierung oder Benzylierung geschützt sein können, oder

b) Umsetzung eines reaktiv veresterten 3,3-Diphenylpropanol der Formel IV



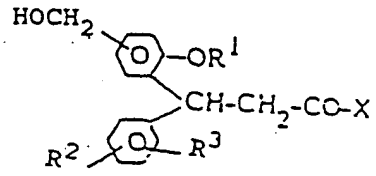
IV

in der R^1 bis R^3 die oben definierte Bedeutung haben und jegliche Hydroxygruppen geschützt sein können, und in der Y eine Abgangsgruppe, vorzugsweise Halogen oder eine Alkyl- oder Arylsulphonyloxygruppe ist, mit einem Amin der Formel V

H - X V

in der X die wie oben definierte Bedeutung hat, oder

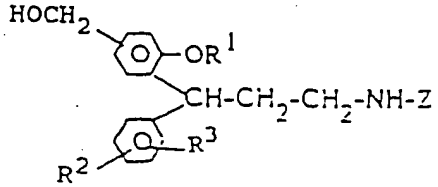
c) Reduktion eines 3,3-Diphenylpropionamids der Formel VI



VI

in der R^1 bis R^3 und X die oben definierte Bedeutung haben und jegliche Hydroxygruppen geschützt sein können, vorzugsweise unter Verwendung eines Komplexmetallhydrids, oder

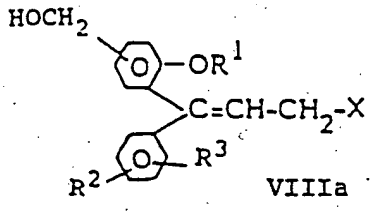
d) N-Methylierung eines sekundären 3,3-Diphenylpropylamins der Formel VII



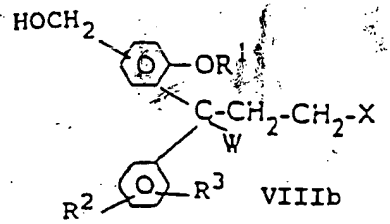
VII

in der R^1 bis R^3 und X die wie oben definierte Bedeutung haben und jegliche Hydroxygruppen geschützt sein können, und in der Z mit Ausnahme von Methyl die gleiche Bedeutung wie R^4 und R^5 hat, wobei Z vorzugsweise eine Kohlenwasserstoffgruppe ist, die wenigstens drei Kohlenstoffatome umfaßt, und wobei die N-Methylierung vorzugsweise unter Verwendung von Formaldehyd oder Ameisensäure durchgeführt wird, oder

e) Reduktion eines 3,3-Diphenylpropenamins der Formel VIIIa oder eines 3,3-Diphenylpropylamins der Formel VIIIb



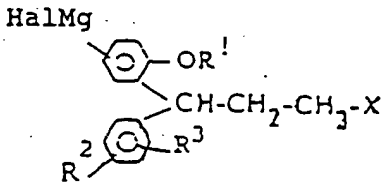
VIIIa



VIIIb

wobei R^1 bis R^3 und X die wie oben definierte Bedeutung haben, und jegliche Hydroxygruppen geschützt sein können, und W für eine Hydroxygruppe oder ein Halogenatom steht, vorzugsweise mittels katalytischer Hydrierung,

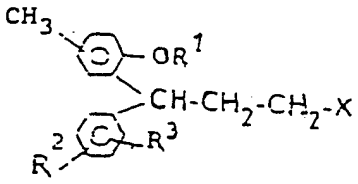
f) Umsetzung eines 3,3-Diphenylpropylamins der Formel IX



IX

in der R^1 bis R^3 und X die wie oben definierte Bedeutung haben, und Hal für Halogen steht, mit Formaldehyd oder einem Formaldehydäquivalent (z.B. s-Trioxan), oder

g) Oxidation der Methylgruppe eines Diphenylpropylamins der Formel X



X

in der R^1 bis R^3 und X die wie oben definierte Bedeutung haben, und

i) falls nötig, Abtrennen der Hydroxyschutzgruppen in den erhaltenen Verbindungen, falls gewünscht, nach der Mono- oder Dihalogenierung eines oder beider Phenylringe(s) 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, Auftrennung eines erhaltenen Gemisches optischer Isomere in die individuellen Enantiomere, und/oder

iv) falls gewünscht, Methylierung einer Orthohydroxygruppe in einer erhaltenen Verbindung der Formel I, in der R^1 Wasserstoff und/oder R^3 Hydroxy ist.

Die Oxidation im oben beschriebenen Verfahren g) kann chemisch, elektrochemisch oder enzymatisch durchgeführt werden. Die chemische Oxidation wird vorteilhafterweise unter Verwendung eines Metallsalzes oder -oxides, wie Cerammoniumnitrat, Manganoxiden, Chromoxi-

den, Vanadiumoxiden, Kobaltacetat, Aluminiumoxid, Wismuthmolybdat, oder Kombinationen davon durchgeführt. Die chemische Oxidation kann auch durch Persäuren mit oder ohne Katalysator oder mit Halogeniden bewerkstelligt werden. Die elektrochemische Oxidation kann mit oder ohne Katalysator durchgeführt werden. Bei enzymatischer Oxidation wird die Verwendung von Bakterien oder Hefen (z.B. Candida guilliermondi, Candida tropicalis) vorgezogen.

Die Entfernung der Hydroxyschutzgruppen nach i) oben kann z.B. durch Behandlung mit Bromwasserstoffsäure, Bortribromid oder durch katalytische Hydrierung erfolgen.

Die Trennung von Gemischen optischer Isomere nach ii) oben in die individuellen Enantiomere kann z.B. durch fraktionelle Kristallisierung der Salze mit chiralen Säuren oder durch chromatographische Trennung auf chiralen Säulen erzielt werden.

Die Ausgangsverbindungen der Formel III und IX können wie in dem unten beschriebenen Herstellungsbeispiel beschrieben, hergestellt werden. Die Ausgangssubstanzen, die in den Verfahren b) bis e) und g) verwendet werden, können wie in der zuvor erwähnten WO 89/06644 (deren Offenbarung durch Bezugnahme hierin aufgenommen wird) beschrieben, hergestellt werden, wobei die Beschreibung im vorliegenden Herstellungsbeispiel sorgfältig in Betracht gezogen werden muß.

Erfindungsgemäß können die Verbindungen der Formel I, in Form der freien Basen oder in Form von Salzen mit physiologisch annehmbaren Säuren, gemäß gebräuchlicher pharmazeutischer Verfahren in geeignete galenische Formen gebracht werden, wie z.B. Mittel zur oralen Verwendung, zur Injektion, zur Verabreichung als Nasenspray oder dergleichen. Derartige erfindungsgemäße pharmazeutische Mittel umfassen eine wirksame Menge der Verbindungen der Formel I in Verbindung mit pharmazeutisch annehmbaren kompatiblen Trägermaterialien oder Verdünnungsmitteln, wie sie dem Fachmann bekannt sind. Die Träger können jegliche inerte, organische oder anorganische Substanzen sein, die für enterale, perkutane oder parenterale Verabreichung geeignet sind, wie z.B. Wasser, Gelatine, Gummi arabicum, Lactose, mikrokristalline Cellulose, Stärke, Natriumstärkeglykolat, Calciumhydrogenphosphat, Magnesiumstearat, Talkum, kolloidales Siliciumdioxid, und dergleichen. Derartige Mittel können auch andere pharmazeutisch aktive Bestandteile und konventionelle Zusätze, wie z.B. Stabilisatoren, Benetzungsmittel, Emulgatoren, Geschmacksstoffe, Puffer und dgl. enthalten.

Die erfindungsgemäßen Mittel können z.B. für orale Verabreichung in fester oder flüssiger Form, wie z.B. in Form von Tabletten, Kapseln, Pulvern, Sirup, Elixieren und dgl. und für parenterale Verabreichung in Form steriler Lösungen, Suspensionen oder Emulsionen oder dgl. hergestellt werden.

Die Verbindungen und Mittel können, wie oben erwähnt, für die gleichen therapeutischen Indikationsgebiete verwendet werden, wie die Verbindungen der oben erwähnten WO 89/06644, d.h. zur Behandlung von Acetylcholin-vermittelten Leiden, wie z.B. Harninkontinenz. Die Dosis der spezifischen Verbindung wird in Abhängigkeit ihrer Wirksamkeit, der Verabreichungsweise,

des Alters und Gewichts des Patienten und des Schweregrades des zu behandelnden Leidens variieren. Die tägliche Dosis kann z.B. im Bereich von 0,01 mg bis etwa 4 mg je Kilogramm Körpergewicht liegen, und in Form einer Einzeldosis oder in Form multipler Gaben, z.B. von etwa 0,05 mg bis etwa 200 mg je Gabe verabreicht werden.

Die Erfindung wird weiter durch das folgende, nichtbeschränkende Beispiel und durch pharmakologische Tests dargestellt werden. Es wird auf die begleitende Zeichnung Bezug genommen werden, wobei die einzige Figur (Figur 1) die Hemmungskurven des Blasendrucks für eine erfindungsgemäße Verbindung bzw. eine im Stand der Technik bekannte Verbindung zeigt.

Allgemeines

NMR-Daten wurden mit einem Jeol JNM-EX 270 Fourier-Transformationsspektrometer erhalten. Die Spektren wurden mit Tetramethylsilan (TMS) als internen Standard bei 30°C aufgenommen. Infrarotspektren wurden mit einem Perkin Elmer 599B-Instrument aufgenommen. Nichtkorrigierte Schmelzpunkte wurden mit einem Koeffler-Gerät erhalten. Die Gaschromatographie wurde mit einem HP 5940-Gerät mit einer 10 m HP-1-Säule und dem im linearen Temperaturgradientenbetrieb geheizten Ofen durchgeführt.

BEISPIEL 1

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin-(+)mandelat und (-)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin(-)mandelat

a) 6-Brom-4-phenyl-3,4-dihydrocumarin

Eine Lösung von p-Bromphenol (138 g, 0,8 mol), Zimtsäure (148 g, 1,0 mol), Essigsäure (200 g) und konzentrierter Schwefelsäure wurde während 2 Stunden unter Rückfluß gekühlt. Flüchtiges Material wurde bei reduziertem Druck destilliert. Der im Rückstand befindliche Sirup wurde abgekühlt und mit kaltem Wasser fein gemahlen. Dies führte zu einer halbkristallinen Masse. Diese wurde in extensiver Weise mit Wasser, gesättigtem Natriumcarbonat und zum Schluß erneut mit Wasser gewaschen. Das Material wurde durch einen gesinterten Glastrichter filtriert, und dann mit einem gleichen Gewicht an Ethanol gemischt. Die Aufschlämmung wurde während einer Stunde bei Raumtemperatur gerührt und dann filtriert. Das erhaltene Produkt wurde kurz mit Ethanol und dann mit Diisopropylether gewaschen. Nach dem Trocknen wurden 135 g (55,7%) der Titelverbindung als weiße Kristalle, die bei 117°C schmelzen, isoliert.

b) Methyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropanonat

6-Brom-4-phenyl-3,4-dihydrocumarin (290 g, 0,96 mol) wurden in einem Gemisch an Methanol (1 l) und Aceton (1 l) aufgelöst. Zu der obigen Lösung wurden Kaliumcarbonat (160 g, 1,16 mol), α-Chlortoluol (140 g, 1,1 mol) und Natriumiodid (30 g, 0,47 mol) zugegeben, und das Gemisch wurde unter Rückflußkühlung während 3 Stunden gerührt. Die Lösung wurde durch Destillation konzentriert, und der Rückstand wurde mit Wasser behandelt und mit Diethylether extrahiert. Die Etherschicht wurde aufeinanderfolgend mit Wasser, mit gesättigter Natriumcarbonatlösung und Wasser gewaschen. Die organische Schicht wurde über Natriumsulfat

getrocknet, filtriert, und dann eingedampft, um dann 420 g (etwa 100%) der Titelverbindung als hellgelbes Öl zu ergeben.

c) 3-(2-Benzyloxy-5-bromphenyl)-3-phenylpropanol

Methyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropanonat (112 g, 0,26 mol) wurde in Tetrahydrofuran (250 ml) gelöst und tropfenweise in einer Stickstoffatmosphäre zu einer Suspension von Lithiumaluminiumhydrid (5,9 g, 0,16 mol) in Tetrahydrofuran (250 ml) gegeben. Das Gemisch wurde über Nacht in Stickstoffatmosphäre gerührt. Das überschüssige Hydrid wurde durch Zugabe einer kleinen Menge an HCl (wässrig, 2 M) gespalten. Die Lösung wurde auf ein Celatomkissen filtriert, und die Feststoffe wurden gründlich mit Ether gewaschen. Die kombinierte Etherlösung wurde mit HCl (2 M), Wasser, Natriumhydroxid (2 M) und dann erneut mit Wasser gewaschen. Die organische Lösung wurde über Natriumsulfat getrocknet, filtriert und eingedampft, um 98,5 g (95%) der Titelverbindung als farbloses Öl zu ergeben. Eine kleine Fraktion des Öls wurde aus Diisopropylether/Petrolether kristallisiert und ergab Kristalle, die bei 70°C schmolzen.

d) 3-(2-Benzyloxy-5-bromphenyl)-3-phenylpropyl-p-toluolsulfonat

Zu einer Lösung von 3-(2-Benzyloxy-5-bromphenyl)-3-phenylpropanol (107 g, 0,24 mol) in Dichlormethan (300 ml) und Pyridin (75 ml) bei 0°C wurde p-Toluolsulfonylchlorid (57 g, 0,3 mol) zugegeben. Die Lösung wurde über Nacht bei 0°C gerührt, und dann bei reduziertem Druck und einer Badtemperatur unterhalb von 50°C eingedampft. Der Rückstand wurde in Wasser gegossen, und dann wurde das Gemisch mit Diethylether extrahiert. Die organische Phase wurde aufeinanderfolgend mit Wasser, HCl (2 M) und Wasser gewaschen und zuletzt über Natriumsulfat getrocknet. Nach der Filtration wurde die Etherlösung bei einer Badtemperatur von <50°C eingedampft, um 137 g (etwa 100%) 3-(2-Benzyloxy-5-bromphenyl)-3-phenylpropyl-p-toluolsulfonat als blaßgelbes Öl zu ergeben.

e) N,N-Diisopropyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropylamin

3-(2-Benzyloxy-5-bromphenyl)-3-phenylpropyl-p-toluolsulfonat (115 g, 0,2 mol) wurde in einem Gemisch von Acetonitril (150 g) und Diisopropylamin (202 g, 2,0 mol) aufgelöst, und das Gemisch wurde während 4 Tagen unter Rückfluß gekühlt. Die Lösung wurde eingedampft, und zu dem entstehenden Sirup wurde Natriumhydroxid (2 M, 200 ml) zugegeben. Das Gemisch wurde konzentriert, abgekühlt und dann mit Diethylether extrahiert. Die Etherphase wurde extensiv mit Wasser gewaschen. Das Amin wurde mit einem Überschuß an Schwefelsäure (1 M) extrahiert. Die wässrige Phase wurde mit Diethylether gewaschen und dann mit Natriumhydroxid (11 M) basisch gemacht. Das Gemisch wurde dann mit Diethylether extrahiert. Die organische Phase wurde mit Wasser gewaschen, über Natriumsulfat getrocknet, filtriert und dann eingedampft, um 78,6 g (78%) N,N-Diisopropyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropylamin als blaßgelbes Öl zu ergeben. Das ^{1}H-NMR-Spektrum stimmte mit der obigen Struktur überein.

f) Auflösung

Zu einer Lösung von N,N-Diisopropyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropylamin (255 g, 0,53 mol) in Ethanol (750 g) wurde L-(+)-Weinsäure (80 g, 0,53 mol) gegeben. Nachdem das ganze Material aufgelöst war, wurde Diethylether (90 g) zugegeben, und die Kristallisierung begann. Nachdem sie über Nacht bei Raumtemperatur gelagert worden waren, wurden die gebildeten Salze abfiltriert, mit frischer Ethanoldiethyletherlösung (2:1) gewaschen und getrocknet, um 98 g weißer Kristalle, die bei 156°C schmelzen, zu ergeben. $[\alpha]^{22} = 16,3°$ (c = 5,1, Ethanol)

Die Mutterlauge aus der Fällung mit L-(+)-Weinsäure wurde eingedampft. Der resultierende Sirup wurde mit Natriumhydroxid (2 M) behandelt und mit Diethylether extrahiert. Die organische Phase wurde mit Wasser gewaschen, über Natriumsulfat getrocknet, filtriert, und dann eingedampft, wodurch 170 g freie Base entstanden. Die Base (170 g, 0,35 mol) wurde in Ethanol (500 ml) gelöst, und es wurde D-(-)-Weinsäure (53 g, 0,53 mol) zugegeben. Nachdem sich alles gelöst hatte, wurde Diethylether (50 ml) zugegeben, und die Kristallisation begann. Die Kristalle wurden abfiltriert und mit frischer Ethanoldiethyletherlösung gewaschen. Es entstanden 105 g Kristalle, die bei 154-155°C schmelzen. $[\alpha]^{22} = -16,4°$ (c = 5,0, Methanol).

Die Mutterlauge wurde konzentriert, basisch gemacht und wie oben behandelt, was zu 80 g freier Base führte. Diese Base wurde in Ethanol gelöst und mit L-(+)-Weinsäure, wie oben beschrieben, behandelt, wodurch weitere 20 g der rechtsdrehenden Form des Salzes entstanden. (Schmelzpunkt 156°C). Auf analoge Weise konnten 20 g der linksdrehenden Form erhalten werden.

Die gesammelte rechtsdrehende Form wurde in Wasser gelöst und mit Natriumhydroxid (2 M) basisch gemacht. Das Gemisch wurde dann mit Diethylether extrahiert. Die organische Phase wurde mit Wasser gewaschen, über Natriumsulfat getrocknet, filtriert, und zuletzt eingedampft, um das chirale Amin (88 g) als farbloses Öl zu ergeben. $[\alpha]^{22} = 16,3°$ (c = 5,1, Ethanol).

Auf analoge Weise wurde die linksdrehende Base erhalten (90 g). $[\alpha]^{22} = -16,1°$ (c = 4,2, Ethanol). Die durch Chromatographie ermittelte optische Reinheit betrug >99%.

g1) <u>(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylaminhydrochlorid</u>

Ein Gemisch von Magnesium (12,2 g, 0,5 mol), Ethylbromid (2 g), und Iod (ein kleiner Kristall) in trockenem Diethylether (200 ml) wurde erwärmt bis die Reaktion begann. (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropylamin (45,6 g, 0,095 mol) und Ethylbromid (32,7 g, 0,3 mol), die in trockenem Diethylether (250 ml) aufgelöst worden waren, wurden dann unter Stickstoffatmosphäre tropfenweise zugegeben. Das Gemisch wurde während 1,5 Stunden unter Rückfluß gekühlt, dann in einem Aceton/Trockeneisbad, in das pulverisiertes Trockeneis (etwa 100 g) vorsichtig zugegeben wurde, gekühlt. Tetrahydrofuran wurde dann zugegeben, wenn es notwendig war zu verhindern, daß das Gemisch fest wurde. Das Reaktions-

gemisch wurde während 0,5 Stunden gerührt, nachdem Ammoniumchlorid (200 ml, 20% Gew./Gew.) zugegeben worden waren. Das Gemisch wurde heftig gerührt bis 2 transparente Phasen entstanden und dann wurde das Gemisch durch ein Celatomkissen filtriert. Die wässrige Schicht wurde mit Diethylether gewaschen und dann mit Salzsäure bis zu einem pH-Wert von 1 angesäuert. Die gefällte halbkristalline gummiartige Masse wurde mit Wasser gewaschen und dann in eine Rundbodenflasche überführt. Das Produkt wurde aufeinanderfolgend mit Aceton, Benzol, Toluol, Diisopropylether und Methanol getrocknet. Die Titelverbindung (35,1 g, 77 %) wurde als bröckelnde glänzende Flocken isoliert und ohne weitere Reinigung verwendet.

g2) (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylaminhydrochlorid

Dieses Produkt wurde in einer Ausbeute von 81% auf entsprechende Weise, wie oben für (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromphenyl)-3-phenylpropylamin beschrieben, isoliert.

h1) (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamin

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamin (34 g, 0,07 mol) wurde in Schwefelsäure (6 g) enthaltendem Methanol (300 ml) gelöst und während 6 Stunden unter Rückfluß gekühlt. Die Lösung wurde dann abgekühlt und konzentriert. Zu dem Gemisch wurden Eiswasser und ein leichter Überschuß einer gesättigten Natriumcarbonatlösung zugegeben. Das Gemisch wurde dann mit Diethylether extrahiert. Die organische Phase wurde mit Wasser gewaschen, über Natriumsulfat getrocknet, filtriert und eingedampft, wodurch 30 g (93%) des Rohesters entstanden. Die Rekristallisierung von Diisopropylether ergab weiße Kristalle, die bei 85-86°C schmelzen. Das ^{1}H-NMR-Spektrum war in Übereinstimmung mit der obigen Struktur.

h2) (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamin

Die Titelverbindung wurde von (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamin auf ähnliche Weise wie oben für das rechtsdrehende Isomer beschrieben in einer 93%igen Ausbeute erhalten.

i1) (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamin

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamin (30 g, 0,065 mol), aufgelöst in Diethylether (250 ml) wurde unter Stickstoff tropfenweise zu einer Suspension von Lithiumaluminiumhydrid (1,9 g, 0,05 mol) in trockenem Diethylether (150 ml) gegeben. Das Gemisch wurde über Nacht bei Raumtemperatur gerührt, und das überschüssige Hydrid wurde durch Zugabe von Wasser (ungefähr 5 g) zersetzt. Das Gemisch wurde während 10 Stunden gerührt, als Natriumsulfat(e) zugesetzt wurde(n). Nach Rühren während 20 Minuten wurde das Gemisch filtriert und dann eingedampft, um 28,4 g der Titelverbindung als farbloses Öl zu ergeben.

i2) (+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamin

Die Titelverbindung wurde auf analoge Weise, wie oben für die linksdrehende Isomerform des (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamin beschrieben, erhalten.

j1) (+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium-(+)mandelat

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamin (28,2 g, 0,065 mol) wurden in Methanol (300 g) gelöst. Raney Nickel (ein Teelöffel) wurde zugegeben, und das Gemisch wurde bei Atmosphärendruck hydriert, bis die theoretische Menge an Wasserstoff verbraucht wurde. Das Voranschreiten der Reaktion wurde durch Gaschromatographie verfolgt. Das Gemisch wurde dann durch ein Celatomkissen filtriert, und das Lösungsmittel wurde durch Eindampfen bei einer Badtemperatur von <50°C entfernt. Das entstehende Öl wurde in Diethylether gelöst, und die Etherlösung wurde mit Wasser gewaschen, über Natriumsulfat getrocknet und eingedampft, um 22,2 g eines farblosen Öls zu ergeben. $[\alpha]^{22} = 16,7°$ (c = 4,9, Ethanol).

Zu dem obigen Öl, das in 2-Propanol (50 g) gelöst war, wurde S-(+)-Mandelsäure (9,6 g, 0,06 mol) in 2-Propanol (50 g) gegeben. Es wurde trockener Diethylether (50 g) zugegeben, und die Lösung wurde während mehrerer Stunden belassen. Die entstehenden schweren weißen Kristalle wurden abfiltriert, und mit einem Gemisch aus 2-Propanol und Diethylether (1:1 Vol./Vol.) gewaschen und dann getrocknet, wodurch 25 g der Titelverbindung, die bei 148°C schmolz, entstanden. $[\alpha]^{22} = 38,3°$ (c = 5,1, Methanol).

Das ^{1}H-NMR-Spektrum war in Übereinstimmung mit der obigen Struktur.

Die chirale Reinheit, wie durch HPLC bestimmt, war >99%.

Elementaranalyse:

Theoretisch: C: 73,0 H: 8,0 N: 2,8 O: 16,2

Gefunden: C: 72,9 H: 8,1 N: 3,0 O: 16,5

j2) (-)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium(-)mandelat

Die Titelverbindung wurde aus (-)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamin analog zu der in j1) oben beschriebenen Weise erhalten.

Elementaranalyse:

Theoretisch: C: 73,0 H: 8,0 N: 2,8 O: 16,2

Gefunden: C: 73,2 H: 8,1 N: 3,0 O: 16,5

Die freie Base hatte eine optische Rotation von $[\alpha]^{22} = -15,5°$ (c = 5,0, Ethanol).

Die l-(-)-Mandelsäure hatte einen Schmelzpunkt von 147-148°C und eine optische Rotation $[\alpha]^{22} = -37,9°$ (c = 4,7, Methanol).

Die durch HPLC bestimmte optische Reinheit betrug >99%.

Pharmakologie

Die pharmakologischen Untersuchungen, die mit einer erfindungsgemäßen Verbindung und drei im Stand der Technik bekannten Verbindungen, die in der oben erwähnten WO 89/06644 beschrieben wurden, werden im folgenden beschrieben. Die folgenden Verbindungen wurden verwendet:

(A) (+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamin, Hydrochlorid (WO 89/06644);

(B) N,N-Diisopropyl-3-bis-(2-hydroxyphenyl)propylaminhydrochlorid (WO 89/06644);

(C) (+)-N,N-Diisopropyl-3-(5-chlor-2-hydroxyphenyl)-3-(2-hydroxyphenylpropylamin, Hydrochlorid (WO 89/06644);

(D) N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin-(-)mandelsäuresalz (Beispiel 1 oben).

Hochgestellte Indexzahlen im folgenden Text beziehen sich auf Literaturstellen, die am Ende der Beschreibung aufgelistet sind.

Muscarinrezeptorbindungsstudien

Die Gewebepräparationen und die allgemein verwendeten Verfahren wurden an anderer Stelle für die Ohrspeicheldrüse[1], die Harnblase[2], das Herz[3] bzw. den cerebralen Cortex[3], im Detail beschrieben. Männliche Meerschweinchen (250-400 g Körpergewicht) wurden durch einen Schlag auf den Nacken getötet und ausgeblutet. Das Gehirn wurde zur Sektion des cerebralen Cortexes (lediglich die graue Substanz) auf Eis gegeben. Harnblasen, Herz und Ohrspeicheldrüsen wurden herausgeschnitten und in einen Krebs-Henseleit-Puffer (pH 7,4), enthaltend 1 mM Phenylmethylsulfonylfluorid (PMSF, ein Proteaseinhibitor), gegeben. Die herausgeschnittenen Gewebe wurden in einem eiskalten Natriumkaliumphosphatpuffer (50 mM, pH 7,4), enthaltend 1 mM PMSF, unter Verwendung eines Polytron PT-10-Gerätes (Blase, Herz, Ohrspeicheldrüse) und eines Potter-Elvehjem-Teflon-Homogenisiergerätes (Cortex) homogenisiert. Zuletzt wurden alle Homogenisate mit dem eiskalten Phosphat/PMSF-Puffer zu einer Endproteinkonzentration von ≤0,3 mg/ml verdünnt und sofort in den Rezeptorbindungsassays verwendet. Protein wurde durch das Verfahren von Lowry et al. (1951)[4] unter Verwendung von Rinderserumalbumin als Standard bestimmt.

Die Muscarinrezeptoraffinitäten der oben identifizierten nichtmarkierten Verbindungen A bis D wurden aus Kompetitionsexperimenten abgeleitet, in denen die Fähigkeit die rezeptorspezifische Bindung von (-)^{3}H-QNB (1-Chinuclidinyl[phenyl-4-^{3}H]benzilat, 32,9 Ci/mmol) zu inhibieren, wie zuvor beschrieben[3,5], verfolgt wurde. Jede Probe enthielt 10 µl (-)^{3}H-QNB (Endkonzentration 2 nM), 10 µl einer Lösung der Testverbindung und 1,0 ml Gewebshomogenisat. Dreifachproben wurden unter Gleichgewichtsbedingungen, d.h. bei 25°C während 60 Minuten (Harnblase), 80 Minuten (Herz und cerebraler Cortex) bzw. 210 Minuten (Ohrspeicheldrüse) inkubiert. Nichtspezifische Bindung wurde in Gegenwart von 10 µM unmarkiertem Atropin be-

stimmt. Die Inkubationen wurden durch Zentrifugation[2] beendet, und die Radioaktivität in den Sedimenten wurde durch Flüssigscintillationsspektrometrie[2] bestimmt.

Die IC_{50}-Werte (die Konzentration unmarkierter Verbindung, die zu 50% Inhibition der rezeptorspezifischen (-)^{3}H-QNB-Bindung führte) wurden graphisch aus den experimentellen Konzentrations-Inhibitionskurven bestimmt. Die Affinitäten, die als Dissoziationskonstanten K_i ausgedrückt werden, wurden durch Korrektur der IC_{50} mit der radioligandeninduzierten parallelen Verschiebung und den Unterschieden in der Rezeptorkonzentration unter Verwendung des Verfahrens von Jacobs et al. (1975)[6] berechnet. Die Bindungsparameter für (-)^{3}H-QNB (K_D und Rezeptordichten), die in diesen Berechnungen verwendet wurden, wurden in getrennten Experimentenserien[1-3] bestimmt. Die für die Blase, das Herz, die Ohrspeicheldrüse bzw. den Cortex erhaltenen Ki-Werte sind in der unten gezeigten Tabelle 1 dargestellt.

Funktionelle in vitro-Studien

Männliche Meerschweinchen mit einem Gewicht von etwa 300 g wurden durch einen Schlag auf das Genick getötet und ausgeblutet. Streifen glatter Muskulatur der Harnblase wurden herausgeschnitten und in eine Krebs-Henseleit-Lösung (pH 7,4) gegeben. Die Streifenpräparationen wurden vertikal zwischen zwei Haken in Thermostat-kontrollierte (37°C) Organbädern (5 ml) montiert. Einer der Haken war einstellbar und mit einem Kraftüberträger (FT 03, Grass Instruments) verbunden. In die Krebs-Henseleit-Lösung wurde kontinuierlich Kohlendioxidgas (93,5% O_2/6,5% CO_2) eingeblasen, um den pH auf einen Wert von 7,4 zu halten. Die isometrische Spannung wurde mittels eines Grass Polygraphen (Modell 79D) aufgezeichnet. Eine Ruhespannung von etwa 5 mN wurde initial an jedem Muskelstreifen angelegt, und man erlaubte den Präparationen sich während wenigstens 45 Minuten zu stabilisieren. Die Ruhespannung wurde wiederholt angeglichen, und die Präparationen wurden mehrfach während des Stabilisierungszeitraumes gewaschen.

Carbachol (Carbamylcholinchlorid) wurde als Standardagonist verwendet. Bei jedem Experiment wurde die Lebensfähigkeit der Präparationen und die Reproduzierbarkeit ihrer kontraktilen Antworten initial durch drei aufeinanderfolgende Zugaben einer submaximalen Konzentration (3×10^{-6} M) Carbachol getestet. Dann wurde eine vollständige Konzentrations-Antwortkurve auf Carbachol durch kumulative Zugabe von Carbachol zum Organbad (d.h. schrittweise Zunahme der Agonistenkonzentration bis die maximale kontraktile Antwort erreicht wurde), gefolgt von Auswaschen und einer Ruheperiode von wenigstens 15 Minuten bevor eine Fixkonzentration der Testverbindung (Antagonist) zum Organbad zugegeben wurde, erzeugt. Nach 60 Minuten Inkubation mit dem Antagonisten wurde eine zweite kumulative Konzentrationsantwortkurve gegenüber Carbachol erzeugt. Die Antworten wurden als Prozent der maximalen Antwort auf Carbachol ausgedrückt. EC_{50}-Werte für Carbachol in Abwesenheit (Kontrolle) und Gegenwart des Antagonisten wurden graphisch abgeleitet und Dosisverhältnisse (r) wurden berechnet. Die Dissoziationskonstanten K_B für Antagonisten wurden unter Verwendung der Gleichung (1)[7] berechnet, in der [A] die Konzentration der Testverbindung ist.

$K_B = [A]/r-1$ (1)

Die K_B-Werte, die für die Verbindungen A, B und D, die oben identifiziert wurden, erhalten wurden, sind in der unten gezeigten Tabelle 1 gezeigt.

Tabelle 1

Testverbindung	K_B nm Blase	K_i nM Blase	K_i nM Herz	K_i nM Ohrspeicheldrüse	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

Funktionelle in vivo-Studien

a) Tierpräparationen

Adulte Katzen wurden intraperitoneal mit Mebumal (42 mg/kg) anästhesiert. Nachdem die Tiere eingeschlafen waren, wurde in die Vene des Vorderfußes eine Infusionskanüle eingeführt, und der Katze wurde alpha-Chloralose verabreicht. Während des Experimentes wurde das Tier auf einen Operationstisch gelegt, der mit einem Feedback-kontrollierten elektrischen Kissen aufgeheizt wurde. Bei der Katze wurde ein Luftröhrenschnitt durchgeführt. Zur Aufzeichnung des Blutdruckes wurde ein Polyethylenkatheter in die Oberschenkelarterie eingeführt, wobei sich die Spitze in der Aorta befand und über den Dreiwegehahn mit einem Blutdruckvermittler und einem Grass-Polygraphen verbunden. Die Herzgeschwindigkeit wurde durch Verbindung eines Gerätes zum Registrieren der Fließgeschwindigkeit der Blutbewegung mit einem Treiberverstärker aufgezeichnet, der das Signal von dem Blutdrucküberträger empfing. Der Blutfluß in der zentralen mesenterialen Arterie wurde durch eine Ultraschallflußsonde um die Arterie, die mit einem Transonic-Blutflußmeter und dann mit einem Grass-Polygraphen zur Aufzeichnung des Flußes verbunden war, gemessen. Zur Infusion der Testsubstanzen, Verbindungen D und A (wie oben definiert) wurde ein Polyethylenkatheter in den Dreiwegehahn in der femoralen Vene eingeführt, und mit einer Spritze verbunden, die sich in einer Infusionspumpe befand (Sage Instrument).

Durch einen Einschnitt in die proximale Harnröhre wurde ein Katheter in die Harnblase eingeführt. Zu Beginn eines jeden Experiments wurde dieser Katheter mit einem offenen Gefäß verbunden, das mit 38°C warmer physiologischer Kochsalzlösung angefüllt war und sich oberhalb des Tieres befand. Während dieses Stabilisierungszeitraumes entspannte sich die Blase, was zu einer Füllung der Blase mit Kochsalz unter konstantem hydrostatischem Druck führte. Nach dem Stabilisierungszeitraum wurde der Blasenkatheter mit einem Druckvermittler zur Aufzeichnung des intravesikalen Drucks verbunden. Der Blutdruck, die Herzgeschwindigkeit, der Blutfluß und der Blasendruck wurden während des ganzen Experiments gleichzeitig und kontinuierlich aufgezeichnet. Man beließ die Tiere während wenigstens 45 Minuten, um einen Gleichge-

wichtszustand in Bezug auf die cardiovaskulären Variablen vor Beginn des Experimentes zu erreichen.

Der Blasendruck wurde 8 Minuten vor dem Ende der Infusion der Testsubstanz gemessen. Die operative Präparation wurde durch intravenöse Injektion von 0,25 µg/kg Körpergewicht Noradrenalin und 0,5 µg/kg Körpergewicht Acetylcholin getestet.

b) Dosierung

Um die Dosis-Wirkungsbeziehung der Verbindung D, die oben identifiziert wurde, zu untersuchen, wurde die Substanz in Dosierungen von 0,000 (physiologische Kochsalzlösung), 0,003, 0,010, 0,030 bzw. 0,100 mg/kg mit Infusionen während 2 Minuten und einem Infusionsvolumen von 1 ml/kg verabreicht. Jede Katze erhielt alle Dosierungen und wurde so behandelt, daß wenigstens 45 Minuten zwischen den 0,003 und 0,010 mg/kg-Dosierung und 60 Minuten zwischen der 0,030 und 0,100 mg/kg-Dosierung verblieben.

c) Statistische Verfahren und Berechnung

Die Ergebnisse werden in absoluten Werten dargestellt, und als Mittelwert ± Standardabweichung berechnet.

d) Ergebnisse

(i) Blutdruck

Im allgemeinen hatte die intravenöse Verabreichung der Verbindung D einen geringen oder keinen Effekt auf den Blutdruck mit Ausnahme der Dosierung von 0,3 mg/kg. Diese Dosierung verursachte einen Anstieg von 10% für den diastolischen Blutdruck bzw. 6% für den systolischen Blutdruck.

(ii) Blutfluß

Die intravenöse Verabreichung der Verbindung D verursachte einen Anstieg des Blutflusses in der superioren mesenterialen Arterie von 8, 17 bzw. 21% für die Dosierungen von 0,003, 0,01 bzw. 0,03 mg/kg. Erneut wurde für die höchste Dosierung (0,3 mg/kg) ein 10%iger Anstieg im Blutfluß beobachtet.

(iii) Herzgeschwindigkeit

Die intravenöse Verabreichung der Verbindung D verursachte eine Abnahme von 9% bei der höchsten Dosierung (0,3 mg/kg).

(iv) Blasendruck

Wie aus Figur 4 entnommen werden kann, führte die erfindungsgemäße Verbindung D zu einer dosisabhängigen Inhibition des Acetylcholin-induzierten Effektes auf die Blase, der etwa 10 mal effizienter war als der Effekt, der aus dem Stand der Technik bekannten Verbindung A.

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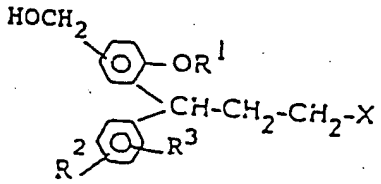
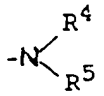
PATENTANSPRÜCHE

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

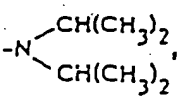
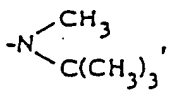
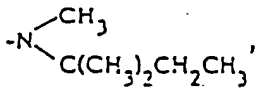
steht, in der jedes R^4 und R^5 unabhängig voneinander für nichtaromatische Kohlenwasserstoffgruppen steht, die eine oder mehrere Hydroxygruppen tragen können und die zusammen wenigstens drei Kohlenstoffatome enthalten und in der R^4 und R^5 miteinander verbunden sein können, um einen Ring zu bilden, 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.

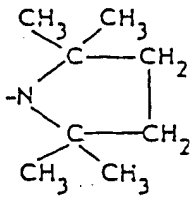
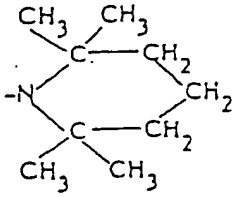
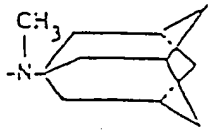
2. 3,3-Diphenylpropylamine nach Anspruch 1, dadurch gekennzeichnet, daß jedes R^4 und R^5 unabhängig voneinander eine gesättigte Kohlenwasserstoffgruppe,

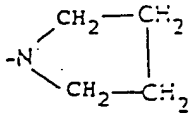
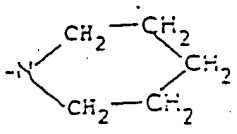
insbesondere eine gesättigte aliphatische Kohlenwasserstoffgruppe, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl bedeutet und R^4 und R^5 zusammen wenigstens drei, vorzugsweise wenigstens vier Kohlenstoffatome umfassen.

3. 3,3-Diphenylpropylamine nach Anspruch 1 oder 2, dadurch g e k e n n z e i c h n e t , 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 g e k e n n z e i c h n e t , 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 g e k e n n z e i c h n e t , 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.

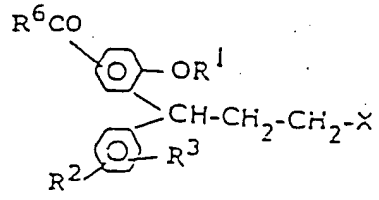
7. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 6 zur Verwendung als pharmazeutisch aktive Substanzen, insbesondere als anticholinerge Mittel.

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

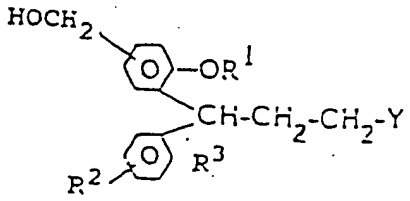


III

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, R^6 Wasserstoff oder R^7O ist, wobei R^7 Wasserstoff, Alkyl, Alkenyl, Alkinyl oder Aryl ist, und jegliche Hydroxy-

gruppen z.B. durch Methylierung oder Benzylierung geschützt sein können oder

b) Umsetzung eines reaktiv veresterten 3,3-Diphenylpropanols der Formel IV



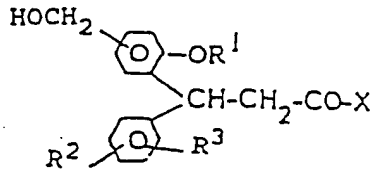
IV

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

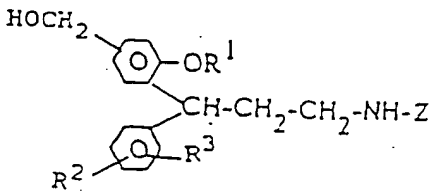
c) Reduktion eines 3,3-Diphenylpropionamids der Formel VI



VI

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können, oder

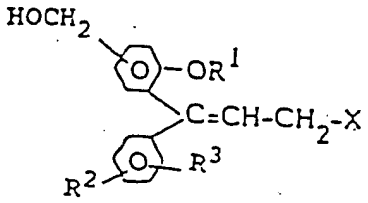
d) N-Methylierung eines sekundären 3,3-Diphenylpropylamins der Formel VII



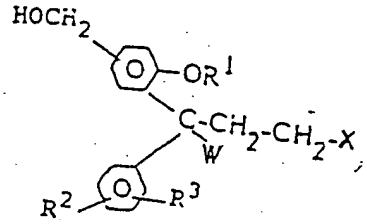
VII

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



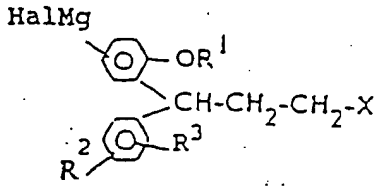
VIIIa



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

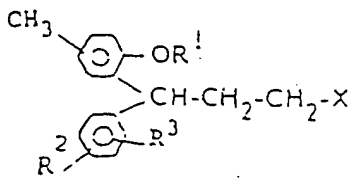
f) Umsetzung eines Diphenylpropylamins der Formel IX



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.

93 924 876.1

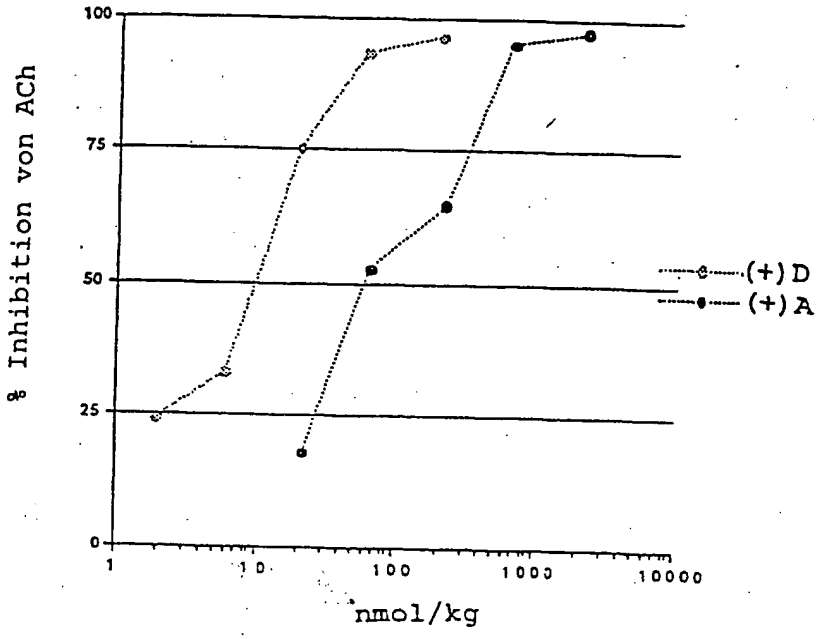


FIG. 1

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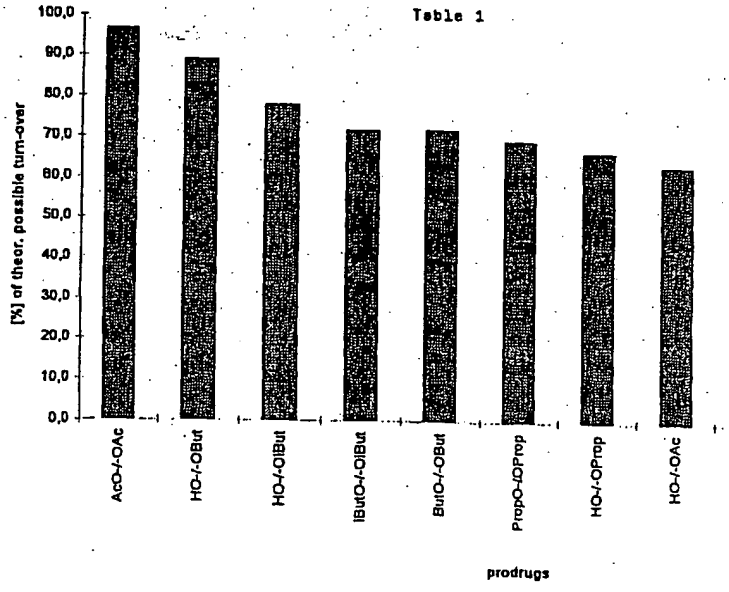
(54) Novel derivatives of 3,3-diphenylpropylamines

(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

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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.

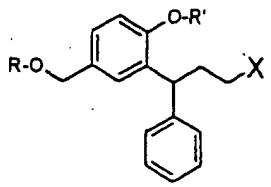
[0007] The document WO 94/11337 discloses that the active metabolite of tolterodine is suggested as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the 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)



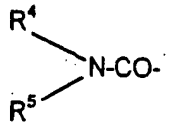
wherein R indepently signifies:

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

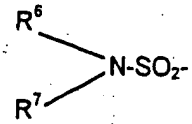
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

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

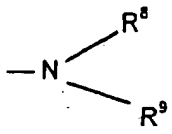
e) a group consisting .



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

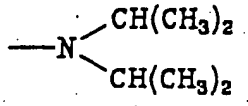
addition salts include the hydrochloride, hydrobromide and the like.

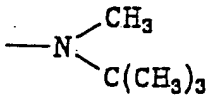
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

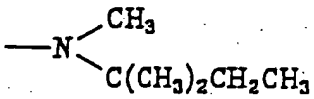
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

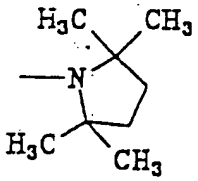
[0014] According to an other embodiment of the invention at least one of R^8 and R^9 comprises a branched carbon chain.

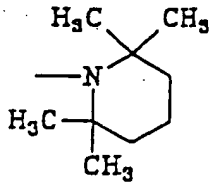
[0015] Presently preferred tertiary amino groups X in Formula I include the following groups a) to h):

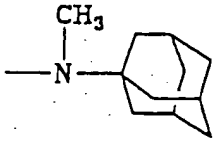
a) 

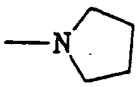
b) 

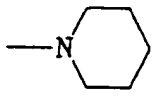
c) 

d) 

e) 

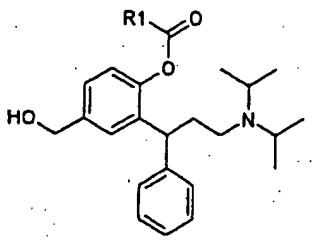
f) 

g) 

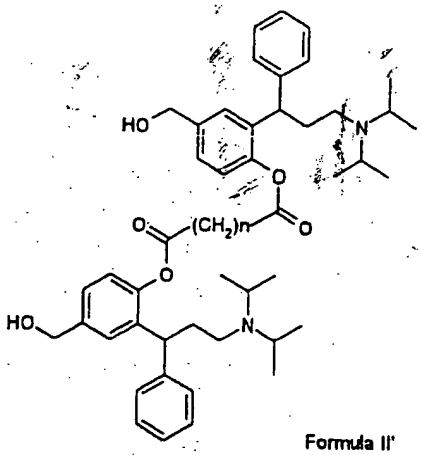
h) 

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

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



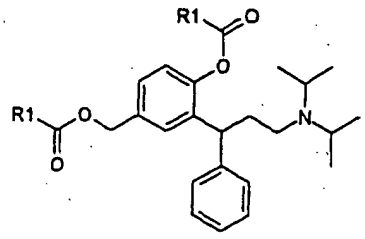
Formula II



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

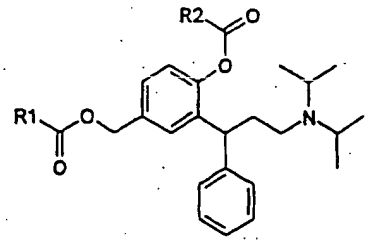
B) Identical diesters represented by the general Formula III



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

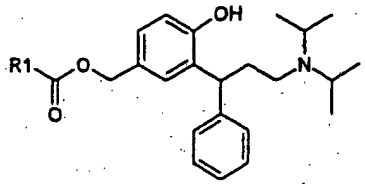
C) Mixed diesters represented by the general Formula IV



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

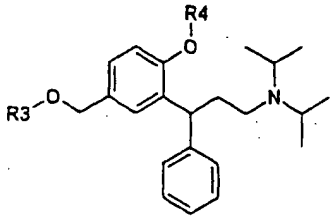
D) Benzylic monoesters represented by the general Formula V



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

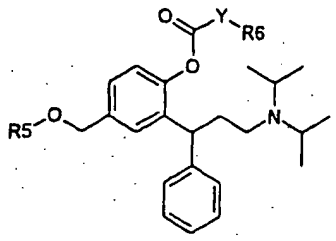
E) Ethers and silyl ethers represented by the general Formula VI



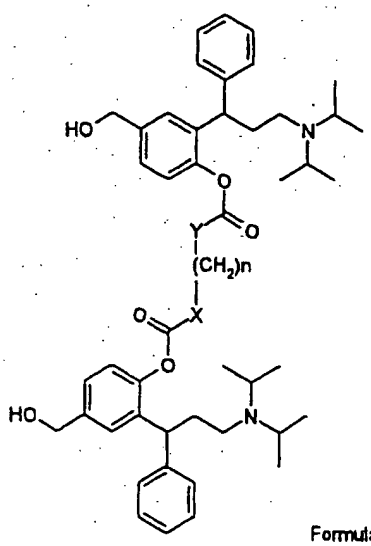
Formula VI

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.

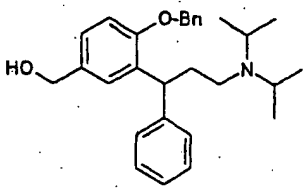
[0024] A solution of the propionate (121.0g) in 350ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9g) in tetrahydrofuran (350ml). After stirring at room temperature for 18h, 20% aqueous HCl was added dropwise and the product was 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.

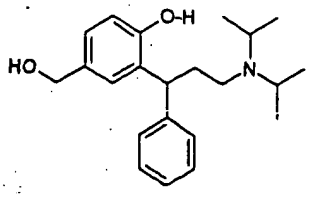
[0027] An ethereal Grignard solution, prepared from the above amine (22.8g), ethyl bromide (17.4g) and magnesium (6.1g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200ml) and then cooled to -60 °C. Powdered solid carbon dioxide (ca. 50g) was the added in small portions and the 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 ($CDCl_3$): 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

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-Cl (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-Cl (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, 128.56, 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

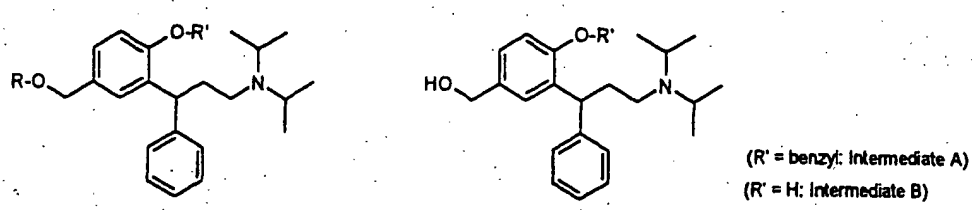
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, (Formula VII', X = Y = NH, n = 4) R_f 0.60 (6); dihydrochloride: m. p. 142.5 - 145.6 °C

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:

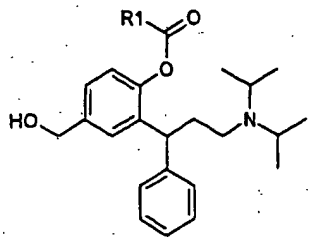
[0039]



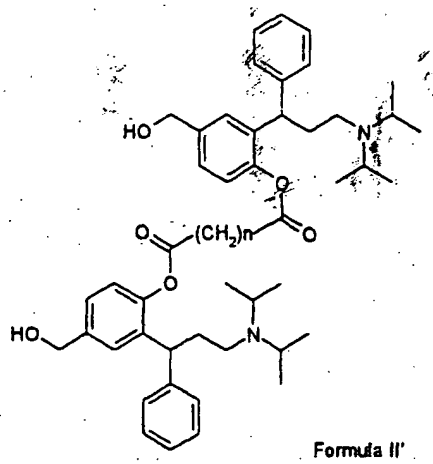
Formula I

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

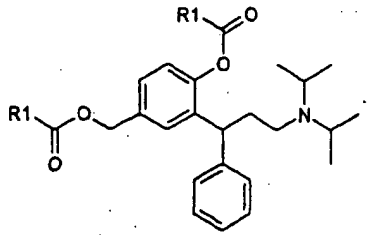


Formula II'

[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

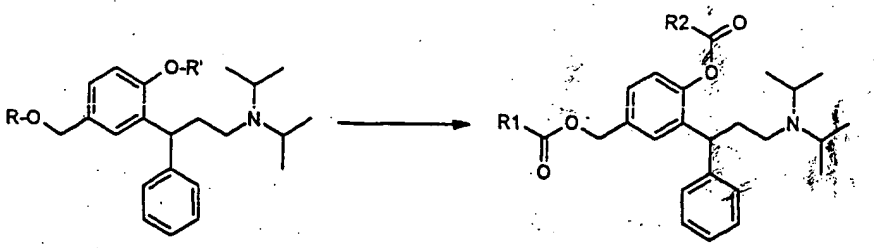
[0042] Di-acyl compounds are readily accessible if an at least two molar excess of acylation agent is used in the above-mentioned conversions of Intermediates A or B or, more general, on treatment of compounds of Formula I with acylating agents in the presence of suitable catalysts.



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.

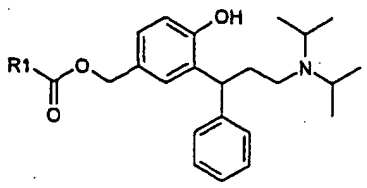


Formula I

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.

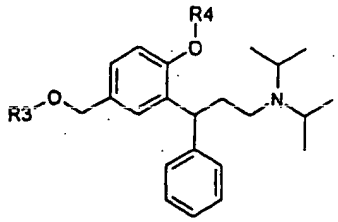


Formula V

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]).



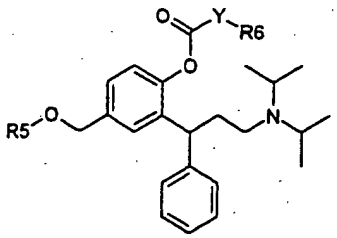
Formula VI

f) Carbamates and Carbonates

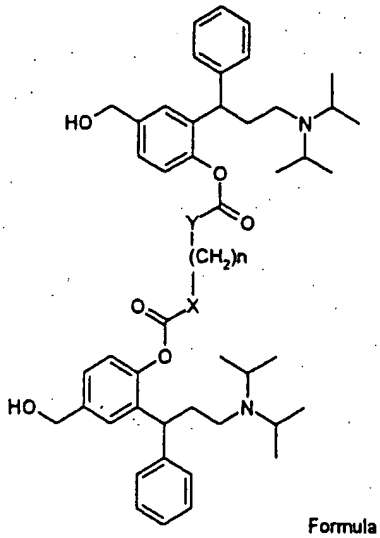
[0046] Other reactive reagents which can be used in the reaction of the hydroxy groups of Intermediates A or B, Formulas II, II', V, or VI (R^3 or R^4 = hydrogen) shown above are, for example, other activated carbonyl compounds or carbonyl precursor reagents.

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.

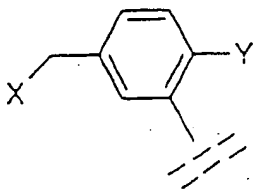
[0055] The analysis was performed by a routine High Pressure Liquid Cromatography (HPLC) method with UV-detection.

[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:

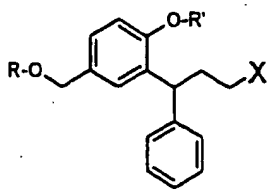


chemical structure X-/-Y

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)

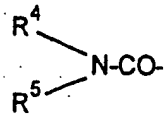
wherein R indepently signifies:

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

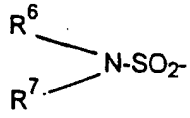
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

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

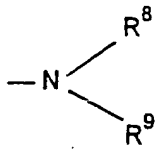
e) a group consisting of



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)

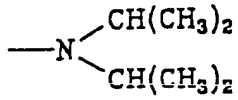
wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, 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

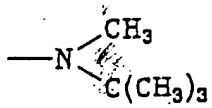
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

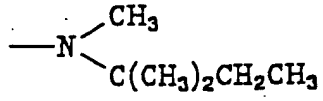
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably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

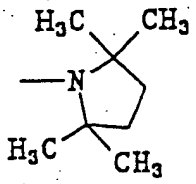
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^8 and R^9 comprises a branched carbon chain.

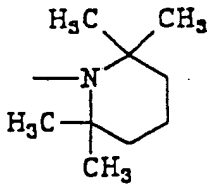
4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

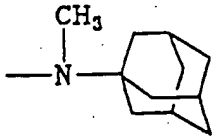
a) 

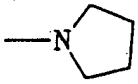
b) 

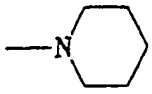
c) 

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

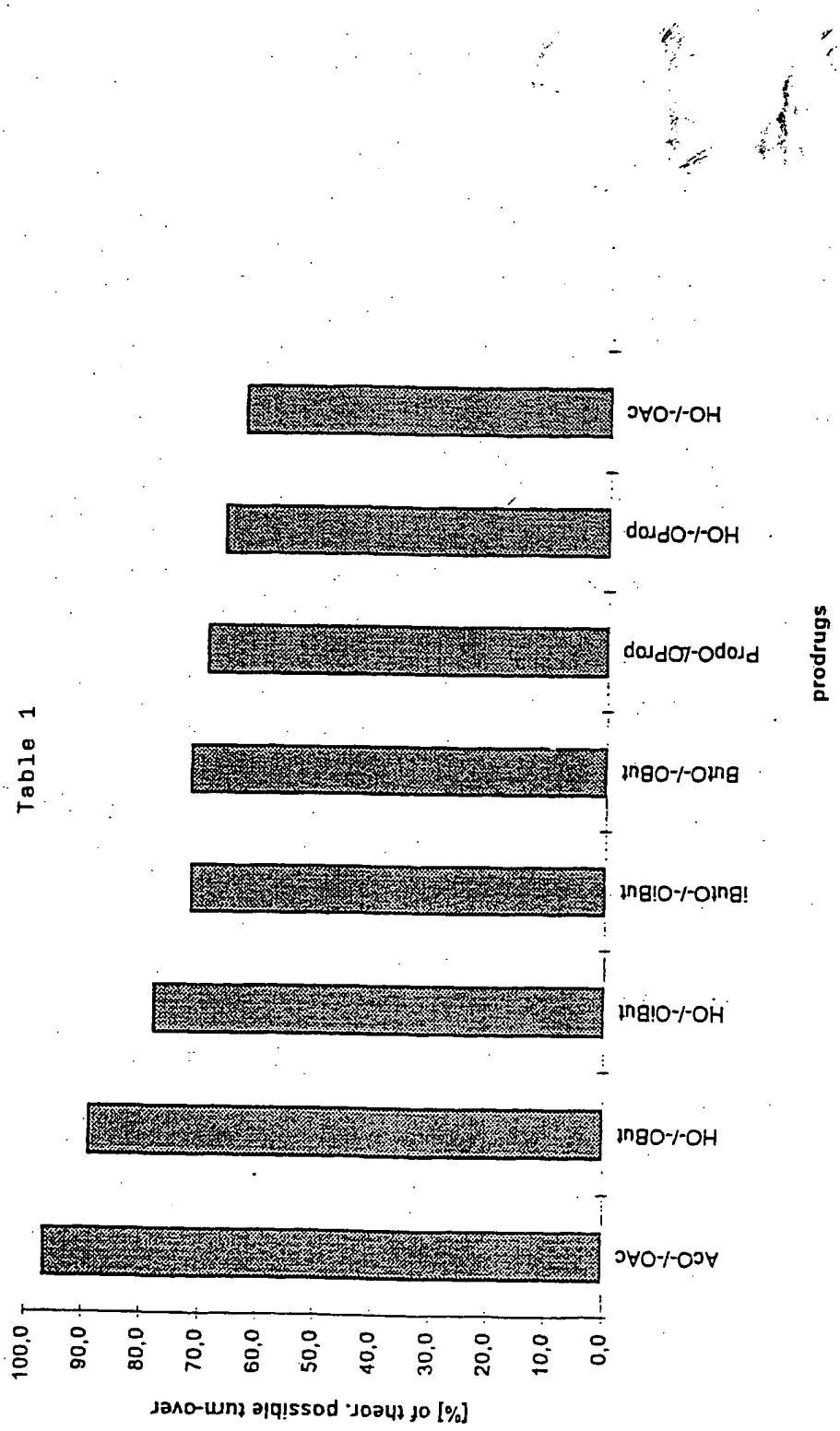
6. 3,3-Diphenylpropylamines according to any one of claims 1 to 5 for use as pharmaceutically active substances, especially as antimuscarinic agents.

7. A pharmac utical 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.

Table 1

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



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
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T : theory or principle underlying the invention
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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
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05-10-1998

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

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EP00/11309

4

Prioritätsbescheinigung über die Einreichung einer Patentanmeldung

Aktenzeichen:	199 55 190.1
Anmeldetag:	16. November 1999
Anmelder/Inhaber:	Schwarz Pharma AG, Monheim/DE
Bezeichnung:	Stabile Salze neuartiger Derivate von 3,3-Diphenyl-propylaminen
IPC:	C 07 C 219/26

Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

München, den 28. September 2000
Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

Jerofsky

A 9161
02/00
EDV-L

Beschreibung

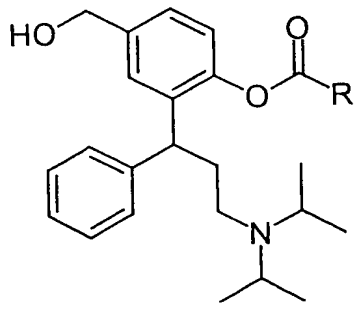
Die vorliegende Erfindung betrifft hochreine, kristalline, stabile Verbindungen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze, Verfahren zu deren Herstellung sowie hochreine, stabile Zwischenprodukte.

Aus dem Dokument PCT/EP99/03212 sind neuartige Derivate von 3,3-Diphenylpropylaminen bekannt.

Sie sind wertvolle Prodrugs für die Behandlung von Harndrang-Inkontinenz und anderen spasmogenen Leiden, die den Nachteil bisher zur Verfügung stehender Wirkstoffe, nämlich zu geringe Absorption der Wirkstoffe durch biologische Membranen oder deren ungünstigen Metabolismus vermeiden.

Weiterhin zeichnen sich diese neuartigen Prodrugs durch verbesserte pharmakokinetische Eigenschaften im Vergleich zu Oxybutynin und Tolterodin aus.

Bevorzugte Verbindungen aus der Gruppe dieser neuartigen Derivate von 3,3-Diphenylpropylaminen sind Ester aliphatischer oder aromatischer Carbonsäuren mit der nachfolgend genannten allgemeinen Formel A



Formel A

in der R die Bedeutung von C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl oder unsubstituiertem oder substituiertem Phenyl hat. Sie können in Form ihrer optischen Isomere, als Racematengemisch und in Form ihrer individuellen Enantiomere vorliegen.

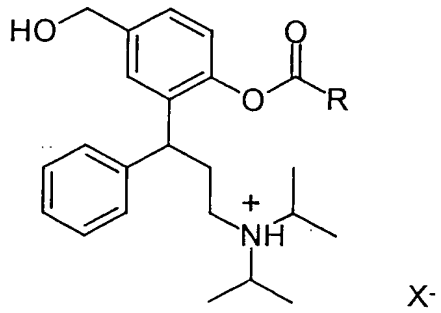
Verbindungen der Struktur der Formel A besitzen allerdings eine geringe Wasserlöslichkeit. Diese verringert ihre orale Bioverfügbarkeit.

Schließlich neigen Monoester der Struktur, wie sie in Formel A wiedergegeben sind, zu intermolekularer Umesterung.

Bei längerer Lagerung ist deshalb unter Gehaltsabnahme von Verbindungen der Struktur der allgemeinen Formel A eine Zunahme von Diester und freiem Diol feststellbar.

Zwar lassen sich grundsätzlich Salze der Verbindungen der allgemeinen Formel A erhalten, indem Lösungen der Verbindungen der Formel A (Basenteil) mit Lösungen von Säuren in jeweils geeigneten Lösungsmitteln vereinigt werden, jedoch erweisen sich die als Festkörper erhaltenen Salze als durchweg amorph und/oder hygroskopisch und sind auch aus den üblichen Lösungsmitteln nicht ohne weiteres kristallisierbar. Derartige Salze weisen eine zu geringe chemische Stabilität auf, um als wertvolle pharmazeutische Wirkstoffe galenisch verarbeitet werden zu können.

Überraschenderweise wurde nun gefunden, daß sich die vorgenannten Nachteile vermeiden lassen, wenn Verbindungen der Struktur der allgemeinen Formel A, nachdem sie unter spezieller Reaktionsführung dargestellt wurden, mit einer physiologisch verträglichen anorganischen oder organischen Säure der allgemeinen Formel H-X, in der ^-X den jeweiligen Säurerest bedeutet, zu ihrem jeweiligen Salz der allgemeinen Formel I umgesetzt werden.



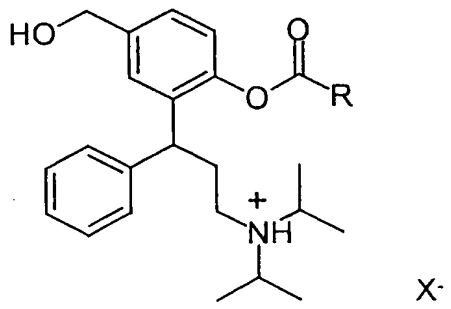
Formel I

Es ist daher Aufgabe der vorliegenden Erfindung, hochreine, kristalline, stabile Verbindugen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze zur Verfügung zu stellen, die die erwähnten Nachteile vermeiden und sich besonders gut zum Einsatz in pharmazeutisch-technischen Formulierungen eignen und zu solchen verarbeiten lassen.

Eine weitere Aufgabe der vorliegenden Erfindung ist es, ein Verfahren zur Herstellung derartiger hochreiner, kristalliner, stabiler Verbindungen in Form ihrer Salze sowie hochreine, kristalline, stabile Zwischenprodukte zur Verfügung zu stellen.

Schließlich ist es Aufgabe der Erfindung, ein Verfahren zur Herstellung der vorgenannten Verbindungen zur Verfügung zu stellen, mit dem die Verfahrensprodukte und die jeweiligen Zwischenprodukte chemo- und regioselektiv in hoher Ausbeute erhalten werden.

Diese Aufgabe wurde dadurch gelöst, daß hochreine, kristalline, stabile Verbindungen der 3,3-Diphenylpropylamine in Form ihrer Salze der allgemeinen Formel I zur Verfügung gestellt werden,



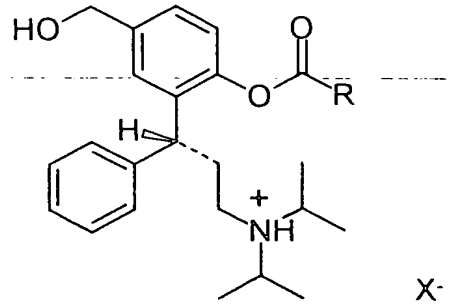
Formel I

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

Nach einer Ausführung der Erfindung können die Salze der allgemeinen Formel I den jeweiligen Säurerest X^- der nachfolgend genannten Säuren enthalten:

Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure.

Nach einer weiteren Ausführungsform der Erfindung werden *R*-konfigurierte Verbindungen der allgemeinen Formel 2 zur Verfügung gestellt,



Formel 2

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

Nach einer vorteilhaften Ausführungsform der Erfindung können die Verbindungen in Form ihrer Salze der allgemeinen Formel 2 den jeweiligen Säurerest X^- der nachfolgend genannten Säuren enthalten:

Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

Bevorzugte Verbindungen der vorliegenden Erfindung sind die Salze

- *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat

und

- *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

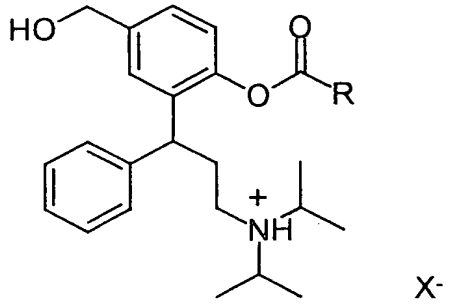
In den Verbindungen der vorliegenden Erfindung bedeutet der Ausdruck „alkyl" vorzugsweise eine geradkettige oder verzweigtkettige Kohlenwasserstoffgruppe mit 1 bis 6 C-Atomen. Besonders bevorzugt sind Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl. Der Ausdruck „Cycloalkyl" bezeichnet zyklische Kohlenwasserstoffgruppen, die 3 bis 10 Kohlenstoffatome aufweisen, die auch geeignete Substituenten anstelle der Wasserstoffatome enthalten können.

Der Ausdruck „Phenyl" bezeichnet eine $-C_6H_5$-Gruppe, die substituiert oder unsubstituiert sein kann. Geeignete Substituenten können Alkyl, Alkoxy, Halogen, Nitro und Amin sein. Der Ausdruck „Alkoxy" hat, bezogen auf den Alkylteil, die gleiche Bedeutung, wie sie bereits oben für „alkyl" angegeben wurde. Geeignete Halogene sind Fluor-, Chlor-, Brom- und Iodatome.

Die vorliegende Erfindung umfaßt auch Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel I sowie wertvoller Zwischenprodukte.

Das Verfahren zeichnet sich durch Chemo- und Regioselektivität sowie hohe Ausbeute aus.

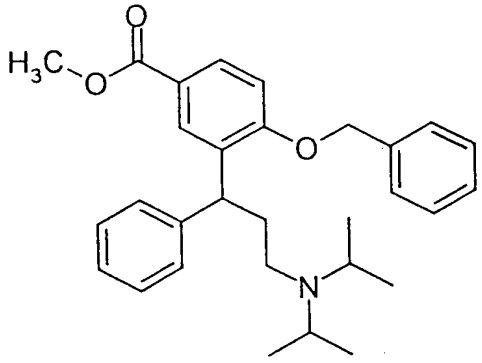
Verbindungen der allgemeinen Formel I



Formel I

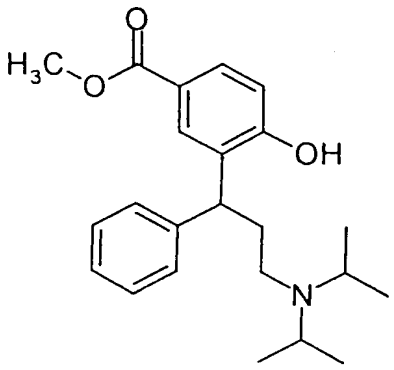
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, werden hergestellt, indem

a) eine Verbindung der Formel III



Formel III

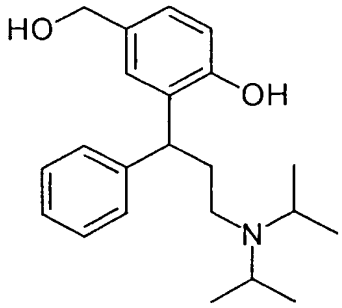
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel V



Formel V

gespalten wird, worauf

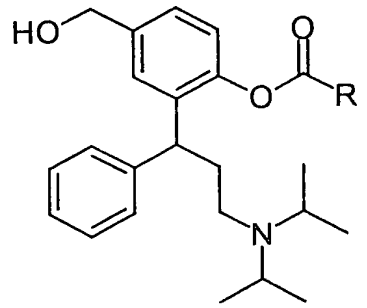
b) die so erhaltene Verbindung der Formel V mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel VI



Formel VI

zu ergeben, die

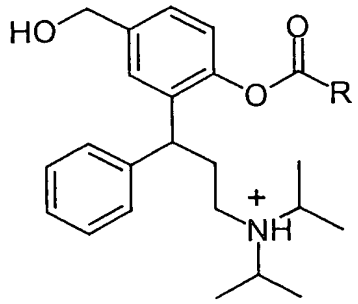
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel A



Formel A

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel I

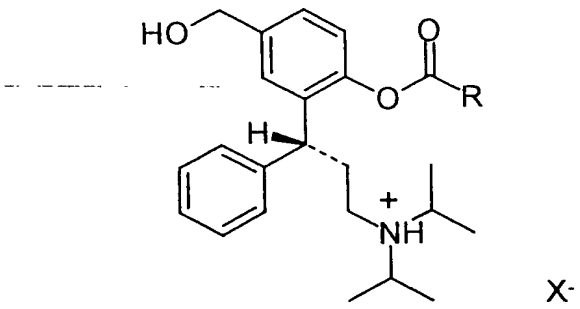


Formel I

umgesetzt wird, worin R für C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

Verfahrensgemäß werden zur Herstellung der Verbindungen der allgemeinen Formel I die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet.

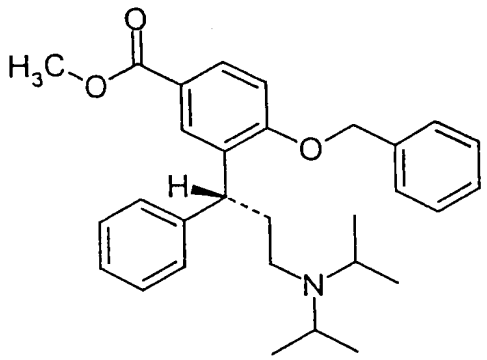
Nach einer vorteilhaften Weiterbildung der Erfindung wird ein Verfahren zur Herstellung von *R*-konfigurierten Verbindungen der allgemeinen Formel 2 beschrieben,



Formel 2

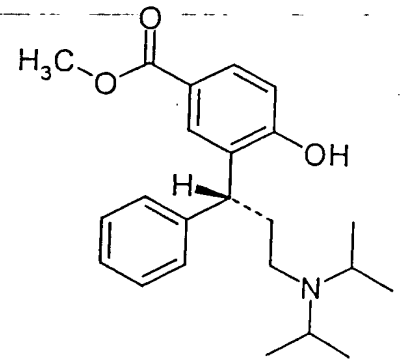
worin R für C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, indem

a) eine Verbindung der Formel 3



Formel 3

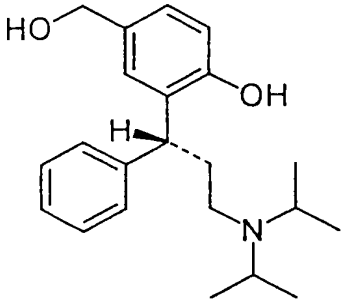
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel 5



Formel 5

gespalten wird, worauf

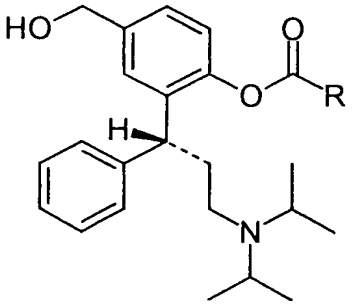
b) die so erhaltene Verbindung der Formel 5 mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel 6



Formel 6

zu ergeben, die

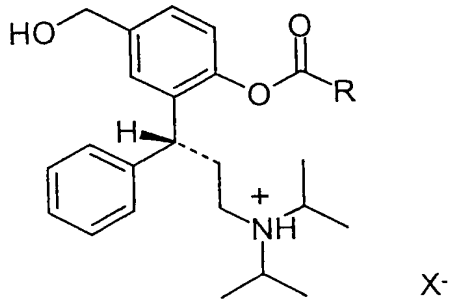
d) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel 1



Formel 1

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel 2



Formel 2

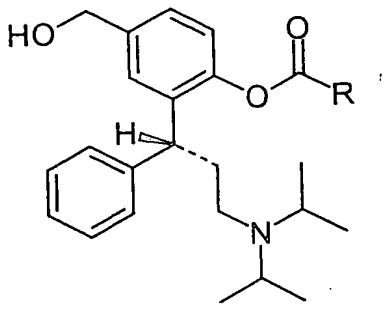
umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

Vorteilhafterweise werden zum Erhalt von Verbindungen der allgemeinen Formel 2 verfahrensgemäß die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet.

Besonders vorteilhaft wird, ausgehend von dem kristallinen *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)benzoesäuremethylester, das hochreine, kristalline Zwischenprodukt *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäure-methylester dargestellt, das zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol reduziert wird, schließlich geeignet acyliert wird und anschließend mit einer

physiologisch verträglichen anorganischen oder organischen Säure unter spontaner Kristallisation zum jeweiligen hochreinen, kristallinen, stabilen Salz umgesetzt wird.

Je nach verwendetem Säurechlorid werden Verbindungen der allgemeinen Formel 1 erhalten,



Formel 1

in der R die Bedeutung von C_1-C_6-alkyl, insbesondere Isopropyl, C_3-C_{10}-cycloalkyl oder unsubstituiertem oder substituiertem Phenyl hat.

Zum Erhalt der erfindungsgemäßen Verbindungen in Form ihrer Salze ist die spezielle Reaktionsführung über besondere Zwischenstufen und individualisierbare Zwischenprodukte entscheidend.

Dies wird anhand des Reaktionsschemas 1 erläutert, in dem Umsetzungen mit *R*-konfigurierten Verbindungen, ohne darauf beschränkt zu sein, beschrieben werden.

Darin bedeuten:

3 = *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure-methylester

4 = *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

5 = *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester

6 = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1 = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester

2a = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester Hydrogenfumarat

2b = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester Hydrochlorid Hydrat

Entsprechend der in den Ausführungsbeispielen erläuterten Reaktionsführung wird die Vorstufe 3 (*R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure-methylester) kristallin und rein dargestellt.

Vorstufe 3 wird nach üblichen Methoden – z.B. BBr_3, $AlCl_3$ - vorzugsweise jedoch mittels Wasserstoffgas über Raney-Nickel in Methanol als Lösungsmittel bei Raumtemperatur (RT) zu 5 (*R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester) gespalten. Dieses fällt in hochreiner, kristalliner Form (Schmp. 143.7 °C) an.

Schließlich wird 5 mit einem geeigneten Reduktionsmittel – z.B. $NaBH_4$/EtOH – vorzugsweise $LiAlH_4$ in einem inerten Lösungsmittel bei niedrigen Temperaturen (-78°C bis + 10°C) reduziert und die Verbindung 6 (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) erhalten. Die Verbindung 6 wird hochrein erhalten und kann aus einem geeigneten Lösungsmittel, wie beispielsweise Ethylacetat, kristallisiert werden. Das farblose feinkristalline Material besitzt einen Schmelzpunkt von 102.3°C. Dies ist insofern überraschend, als die Verbindung 6 im Stand der Technik als amorpher Festkörper beschrieben wird.

Verbindung 6 wird nun in sehr guter Ausbeute und Regio- und Chemoselektivität, zu einem phenolischen Ester acyliert. Diese Reaktion wird bei RT oder niedrigen Temperaturen mit einem Äquivalent Säurechlorid in Gegenwart einer Base in geeigneten Lösungsmitteln ausgeführt. Geeignete Lösungsmittel sind Ethylacetat, Dichlormethan, Tetrahydrofuran, Acetonitril oder Toluol.

Bevorzugt wird die Reaktion mit Isobutyrylchlorid als Säurechlorid und Triethylamin als Base bei den oben angegebenen Temperaturen durchgeführt. Das dann erhaltene 1 (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester) fällt in so hoher Reinheit an, daß mit Lösungen der Fumarsäure in geeigneten Lösungsmitteln spontane Kristallisation unter Bildung des Hydrogenfumarat-Salzes 2a einsetzt.

Dieses Salz zeigt einen scharfen Schmelzpunkt von 103°C, ist bei RT stabil, nicht hygroskopisch und schließt kein Kristallösemittel ein. Es läßt sich beliebig oft umkristallisieren.

Wird anstatt Fumarsäure wasserfreie Salzsäure – z.B. als etherische Lösung – verwendet, tritt ebenfalls Salzbildung unter Erhalt des kristallinen Produktes 2b (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat ein.

Nach erneuter Umkristallisation weist das Produkt 2b einen Schmelzpunktsbereich von 97 – 106°C auf.

Schließlich kann das Produkt 2b ganz besonders vorteilhaft durch die folgende Variante der inversen Reaktionsführung, ausgehend von der Verbindung 6 des Reaktionsschemas 1 direkt erhalten werden. Das Produkt 2b ist damit ohne Zusatz einer externen säurefangenden Base erhältlich, wie nachfolgend erläutert wird.

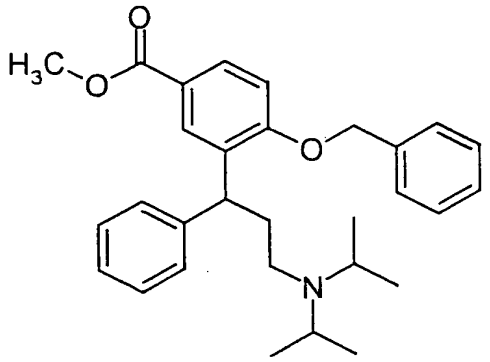
Lösungen von 6 (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) werden in Lösungen von Isobuttersäurechlorid getropft, so daß unter geeigneten Polaritätsbedingungen rasch das wasserfreie Produkt 2b auskristallisiert. 2b ist sehr hygroskopisch.

Wird die vorgenannte Reaktion in feuchten Lösungsmitteln durchgeführt, die mindestens ein Moläquivalent Wasser enthalten, wird direkt ein stabiles und kristallines, hydrathaltiges Produkt 2b erhalten, das die oben genannten Schmelzeigenschaften aufweist.

Die erfindungsgemäßen Verbindungen der allgemeinen Formeln I und 2 eignen sich als Schüttgut.

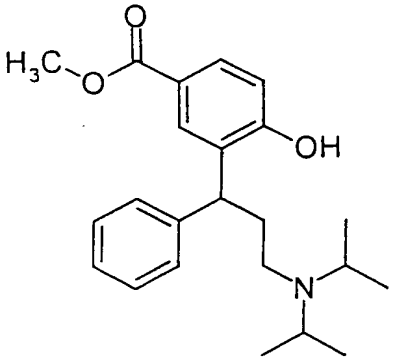
Besonders vorteilhaft sind die hochrein erhältlichen Verbindungen der allgemeinen Formeln III, V, VI, 3, 5 und 6.

Verbindung der Formel III



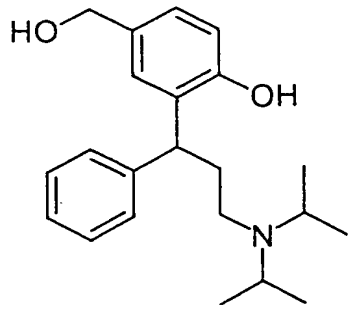
Formel III

Verbindung der Formel V



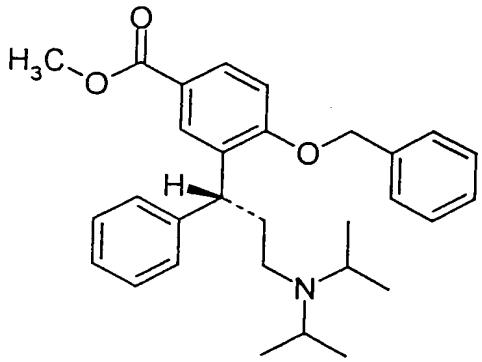
Formel V

Verbindung der Formel VI



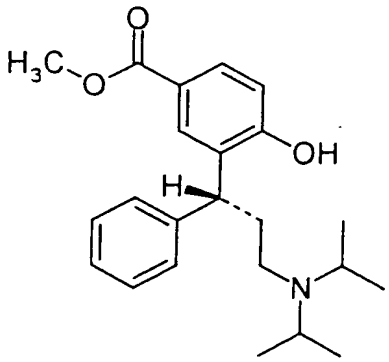
Formel VI

Verbindung der Formel 3



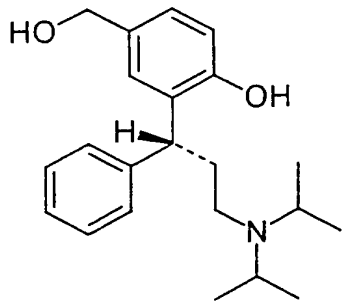
Formel 3

Verbindung der Formel 5



Formel 5

Verbindung der Formel 6



Formel 6

Die vorgenannten Verbindungen III, V, VI, 3, 5, und 6 eignen sich besonders zur Verwendung als jeweils hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

Besonders vorteilhaft eignen sich diese Verbindungen zur Verwendung als Zwischenprodukt bei der Herstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

Schließlich kann das Verfahren besonders vorteilhaft ausgeführt werden, indem eine Verbindung der allgemeinen Formel 6 (siehe Reaktionsschema 1) mit einem Äquivalent Isobutyrylchlorid in Gegenwart von Triethylamin unter Verwendung eines der jeweiligen Lösungsmittel Ethylacetat, Dichlormethan, Tetrahydrofuran, Acetonitril oder Toluol regio- und chemoselektiv zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester umgesetzt wird.

Verfahrensgemäß eignet sich besonders vorteilhaft *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester zur Umsetzung mit Fumarsäure oder Salzsäure unter Bildung des jeweiligen Salzes.

Die nachfolgenden Ausführungsbeispiele erläutern die Erfindung.

Experimentelles

I. Allgemeines

Alle Verbindungen wurden vollständig durch ^{1}H und ^{13}C NMR-Spektroskopie charakterisiert (Bruker DPX 200). Die angeführten chemischen Verschiebungen in den ^{13}C-NMR-Spektren (50 MHz, ppm Werte aufgeführt) beziehen sich auf die Lösungsmittelresonanzen von $CDCl_3$ (77.10 ppm). ^{1}H NMR Daten ($CDCl_3$; 200 MHz, ppm) beziehen sich auf internes Tetramethylsilan).

Dünnschichtchromatographie (DC, R_f angegeben) wurde durchgeführt auf 5x10 cm E. Merck Kieselgelfolien (60F254), die Flecken wurden visualisiert durch Fluoreszenzlöschung oder Ansprühen mit alkalischer Kaliumpermanganatlösung.

Laufmittelsysteme waren: (1), n-Hexan / Aceton / Triethylamin (70/20/10, v/v-%); (2), Toluol / Aceton / Methanol / Essigsäure (70/5/20/5, v/v-%).

Die optischen Drehungen wurden bei einer Wellenlänge von 589.3 nm (Natrium D-Linie) vermessen, bei Raumtemperatur unter Verwendung des Lösungsmittels Ethanol (Gerät: Perkin Elmer Polarimeter Type 241),
Schmelzpunkte (Schmp., in °C) sind unkorrigiert und wurden am Gerät Mettler FP 1 bestimmt, bzw. Differentialthermoanalyse (DSC) am Perkin Elmer Modell DSC7, Auswertungssoftware „Pyris".

UV/VIS-Messungen wurden am Spektrophotometer Modell Lambda 7 (Perkin-Elmer) bei einer Schichtdicke von 1 cm durchgeführt. Angegeben ist die spezifische Absorption einer 1-%igen Lösung ($A^{1\,\%}_{1\,cm}$).

IR-Spektren wurden an einem Perkin-Elmer FTIR Spektrometer Serie 1610 aufgezeichnet (Auflösung 4 cm^{-1}).

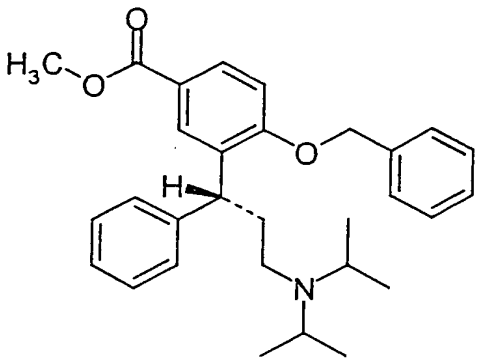
Gaschromatographie-Massenspektrometrie (GC-MS, m/z-Werte und relative Intensität bezogen auf das Basision (%)) wurde mit einem Finnigan TSQ 700 Triple Mass Spectrometer im positiv (P-CI) oder negativ (N-CI) chemische Ionisationsmeßbetrieb mit Methan oder Ammoniak als Reaktantgas bzw. über Elektronenstoßionisation aufgenommen. Hydroxyverbindungen wurden als Trimethylsilylether-Derivate vermessen.

Gekoppelte Flüssigkeitschromatographie-Massenspektrometrie (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z-Werte und relative Intensität (%) werden über einen Massenbereich von 50-500 a.m.u. angegeben.

II. Ausführungsbeispiele

Die in Klammern gesetzten arabischen Zahlen (3), (4), (5), (6) beziehen sich auf die identischen Bezeichnungen im Reaktionsschema 1.

1. Darstellung von
R-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäuremethylester (3)



Eine Lösung von *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure Hydrochlorid (2.30 kg, 4.77 Mol) in 26.4 Liter Methanol und 0.25 Liter konzentrierter Schwefelsäure wird 16 Stunden unter Rückfluß erhitzt. Anschließend wird ein Drittel des Lösungsmittels abdestilliert, abgekühlt und unter Rühren mit 5 kg Eis und 2.5 Liter 25%-iger wässriger Kaliumcarbonatlösung versetzt. Der Ansatz wird erst mit 15 Liter, dann nochmals mit 5 Liter Dichlormethan extrahiert. Die organischen Phasen werden vereinigt und am Rotationsverdampfer zur Trockene eingeengt. Man erhält 1.99 kg

(90.7 % der Theorie) hellgelbes Öl in ca. 90 % Reinheit (DC, NMR).

DC (1): 0.58

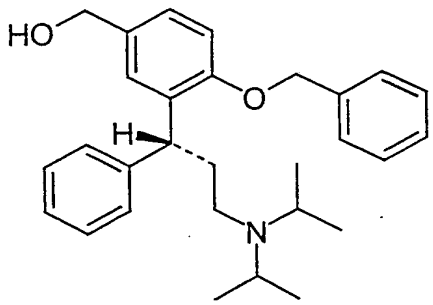
^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.83, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22, 129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Umkristallisation

69.0 g öliges Rohprodukt werden in 150 ml siedendem Methanol gelöst. Nach dem Zusatz von 15 ml destilliertem Wasser wird bei 0°C belassen, wobei sich farblose Kristalle abscheiden. Diese werden abfiltriert, mit wenig kaltem Methanol gewaschen und im Vakuum getrocknet. Ausbeute: 41.8 g (60.6 % der Theorie) farblose Kristalle, Schmp. 89.8 °C; $[\alpha]_D^{20}$ = - 30.7 (c = 1.0, Ethanol).

2. Darstellung von

R-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)



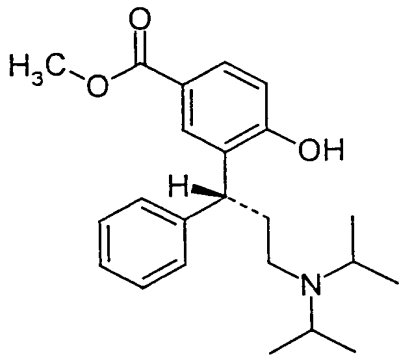
Rohprodukt (3) (28 g) wird in 230 ml absolutem Diethylether gelöst und unter Rühren in eine Suspension von 1.8 g Lithiumaluminiumhydrid in Diethylether (140 ml) getropft. Nach 18 Stunden Rühren bei Raumtemperatur werden tropfenweise 4.7 ml Wasser zugesetzt. Die organische Phase wird abgetrennt, mit wasserfreiem Natriumsulfat getrocknet, filtriert und am Rotationsverdampfer zur Trockene eingeengt. Man erhält 26 g (98.9 % der Theorie) *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) als farbloses Öl.

DC (2): 0.32; $[\alpha]_D^{20}$ = + 6.3 (c = 1.0, Ethanol).

^{13}C-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.

3. Darstellung von

R-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester (5)



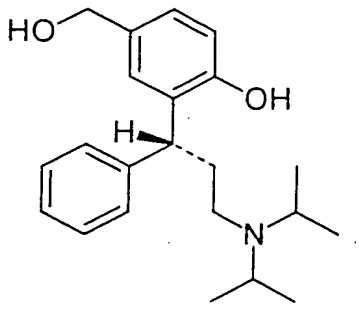
Zu einer gerührten Suspension von 5 g Raney-Nickel (mit Wasser, dann mit Methanol gewaschen) in 200 ml Methanol werden 10 g (21.8 mmol) *R*-(-)-4-Benzyloxy-3-(3-di-isopropylamino-1-phenyl-propyl)-benzoesäuremethylester (3) zugesetzt. Nach kurzem Erwärmen, um alles (3) vollständig zu lösen, wird die Apparatur unter eine Atmosphäre von Wasserstoffgas gesetzt. Nach drei Stunden Rühren bei Normaldruck und Raumtemperatur zeigt die Dünnschichtchromatographie vollständige Umsetzung. Der Ansatz wird mit Stickstoffgas gespült und nach Zusatz von etwas Aktivkohle filtriert. Nach dem Einengen der methanolischen Lösung am Rotationsverdampfer verbleiben 6.0 g (75 % der Theorie) *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester (5) in Form farbloser Kristalle in einer Reinheit von 99.6 % (HPLC).

Schmp. 143.7 °C; DSC 144.7°C

$[\alpha]_D^{20}$ = - 26.6 (c = 0.93, Ethanol).

^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Darstellung von
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Ausgehend von der Zwischenstufe (4), *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) werden in 220 ml Methanol gelöst und mit Raney-Nickel (5 g) versetzt. Die Apparatur wird mit Wasserstoffgas gespült und der Ansatz zwei Tage bei Raumtemperatur gerührt. Nach dem Zusatz von weiteren 5 g Raney-Nickel wird zwei weitere Tage bei Raumtemperatur unter Wasserstoffgasatmosphäre gerührt, vom Katalysator abfiltriert und das Filtrat am Rotationsverdampfer zur Trockene eingeengt. Der ölige, blaßgelbe Rückstand wird in 100 ml Diethylether gelöst, zweimal mit je 100 ml Wasser gewaschen, über Natriumsulfat getrocknet, filtriert und zur Trockene eingeengt. Man erhält 14.1 g (90.4 % der Theorie) *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol in Form eines cremefarbenen, amorphen Festkörpers. Umkristallisation siehe unten c).

b) Ausgehend von der Zwischenstufe (5); *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester

Eine Lösung von 370 mg (1.0 mmol) *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester in 20 ml wasserfreiem Tetrahydrofuran wird langsam und bei Raumtemperatur zu einer gerührten Mischung von trockenem Tetrahydrofuran (10 ml) und einer 1M Lösung von Lithiumaluminiumhydrid in Tetrahydrofuran (3 ml) (unter Stickstoffschutzgasatmosphäre) getropft. Überschüssiges Hydrid wird durch tropfenweisen Zusatz einer gesättigten Natriumcarbonatlösung zersetzt. Nach dem Abtrennen der organischen Phase wird diese am Rotationsverdampfer eingeengt und anschließend

im Hochvakuum getrocknet. Es werden 274 mg (74 % der Theorie) blaßgelbes Öl erhalten, das sich langsam zu einer amorphen Masse verfestigt.

c) Umkristallisation:

Rohprodukt 6 (1.0 g) wird in Ethylacetat gelöst und am Rotationsverdampfer erneut eingeengt. Das so von Fremdlösemitteln (Diethylether bzw. Tetrahydrofuran, s.o.) befreite Diol wird unter leichtem Erwärmen mit 1.5 ml Ethylacetat versetzt. Man rührt, bis eine klare Lösung entstanden ist, läßt auf Raumtemperatur abkühlen und setzt einige Impfkristalle zu. Letztere werden gewonnen, indem rohes 6 über HPLC gereinigt wird, die Hauptfraktion aufgefangen wird, eingeengt und der Rückstand mehrere Stunden im Hochvakuum getrocknet wird. Nachdem deutliche Kristallisation eingetreten ist, beläßt man bei – 10 °C. Die Kristalle werden noch in der Kälte abgesaugt und im Vakuum getrocknet. Man erhält farblose Kristalle in 84 % Ausbeute.

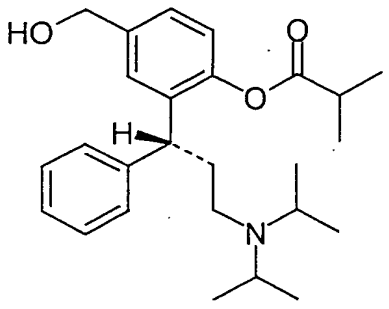
Schmp. 102.3 °C

DC (1): 0.57

$[\alpha]_D^{20}$ = + 21.3 (c = 1.0, Ethanol).

^{13}C-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.

5. Darstellung von
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester (1)

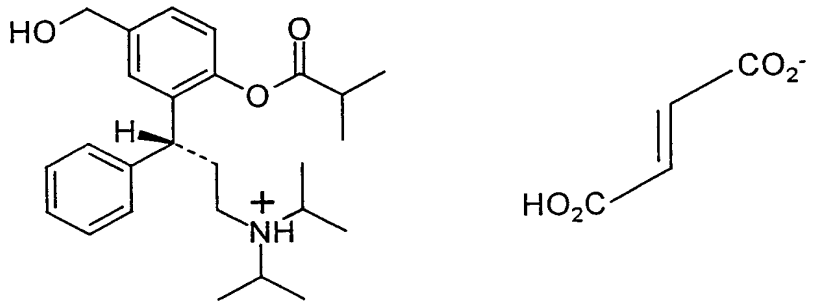


Eine Lösung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) und Triethylamin (20.4 g, 201.7 mmol) in 750 ml Dichlormethan wird unter Rühren und Kühlung (-5 °C) mit einer Lösung von Isobuttersäurechlorid (23.4 g, 201.7 mmol) in 250 ml Dichlormethan versetzt. Nach der Zugabe wird noch 15 Min. bei 0 °C, dann 30 Min. bei Raumtemperatur gerührt und nacheinander mit Wasser (250 ml) und 5%-iger wässriger Natriumhydrogencarbonat-Lösung gewaschen. Die organische Phase wird abgetrennt und am Rotationsverdampfer zur Trockene eingeengt. Der Ester *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester wird als farbloses, viskoses Öl erhalten; Ausbeute: 77.1 g (98.4 % der Theorie).

DC (1): 0.26; $[\alpha]_D^{22}$ = + 2.7 (c = 1.0, Ethanol).

^{13}C-NMR ($CDCl_3$):19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125.59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Darstellung von
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat



Eine Lösung von 41.87 g (102 mmol) *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester in 90 ml 2-Butanon wird unter Erwärmen mit Fumarsäure (11.81 g, 102 mmol) versetzt. Nach dem Lösen der Säure wird langsam unter Rühren Cyclohexan (20-30 ml) bis zum Einsetzen einer Trübung zugesetzt. Man beläßt den farblosen, homogenen Ansatz zunächst 18 Stunden bei Raumtemperatur, dann

mehrere Stunden bei 0 °C. Die ausgefallenen farblosen Kristalle werden abgesaugt, mit wenig Cyclohexan/2-Butanon (90:10, Vol.-%) gewaschen und im Vakuum bei 30 °C getrocknet. Man erhält 44.6 g (83.1 % der Theorie) des Hydrogenfumarat-Salzes des *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester in Form farbloser Plättchen.

Schmp. 98.8 °C, eine zweite Kristallisation aus dem gleichen Lösungsmittelgemisch ergibt das Produkt mit einem Schmp. von 103 °C.

$[\alpha]_D^{20}$ = + 6.0 (c = 1.0, Ethanol).

Elementaranalyse: Berechnet für $C_{30}H_{41}NO_7$ (Molgewicht 527.66) C 68.29 %, H 7.83 %, N 2.65 %, O 21.2 %; gefunden C 68.29 %, H 7.90 %, N 2.72 %, O 21.0 %.

UV/VIS bei λ in nm ($A^{1\%}_{1\,cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

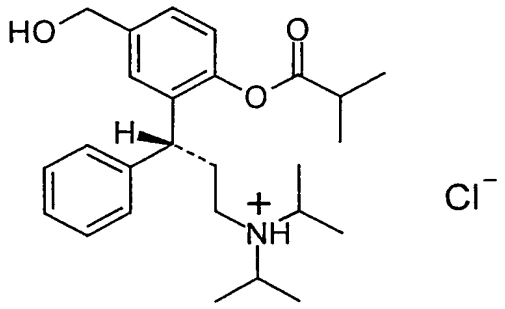
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 ($\underline{C}H_2OH$); 6.832 (=CH, Fumarat); 6.84-7.62 (Aryl, = CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CH\underline{C}H_2$); 34.09 ($\underline{C}H$-C=O); 41.87 ($CH\underline{C}H_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, Fumarat); 170.48 (C=O, Fumarat); 175.62 (i-Pr-C=O).

MS im Direkteinlaß, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Darstellung von
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat



Eine Lösung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester (8.54 g, 25.0 mmol) in 50 ml Dichlormethan wird bei 0°C langsam in eine gerührte Lösung von Isobuttersäurechlorid (2.66 g, 25.0 mmol) in 100 ml Dichlormethan getropft. Nach einer Stunde wird die Kühlung entfernt und noch eine Stunde bei Raumtemperatur nachgerührt. Nach dem Abziehen der flüchtigen Bestandteile im Vakuum am Rotationsverdampfer hinterbleibt ein farbloser, amorph-fester Schaum. Dieser Rückstand wird in Aceton (17 ml) gelöst, mit 0.45 bis 0.50 g Wasser und Diethylether versetzt (ca. 20 – 25 ml) bis deutliche Trübung eintritt. Nach kurzer Behandlung mit Ultraschall tritt spontane Kristallisation ein und es werden unter Rühren langsam weitere 80 ml Diethylether zugetropft. Die ausgefallenen farblosen Kristalle werden abgesaugt und über Nacht im Vakuum über Phosphorpentoxid getrocknet. Man erhält 10.5 g (93.7 % der Theorie) farblos kristallines *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat in 97.0 % Reinheit (HPLC).

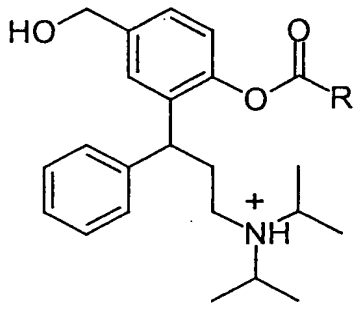
Schmp. 97.1 °C.

$[\alpha]_D^{20}$ = + 4.3 (c = 1.03, Ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

Patentansprüche

1. Verbindungen der allgemeinen Formel I

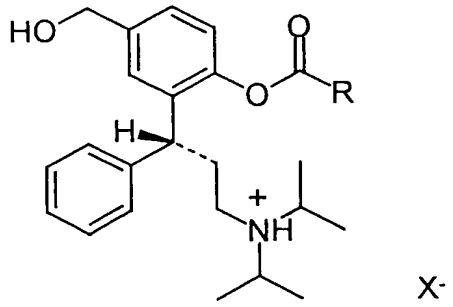


Formel I

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

2. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß X^- jeweils ein Säurerest der Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

3. Verbindungen nach Ansprüchen 1 und 2, dadurch gekennzeichnet, daß sie die allgemeine Formel 2 besitzen,



Formel 2

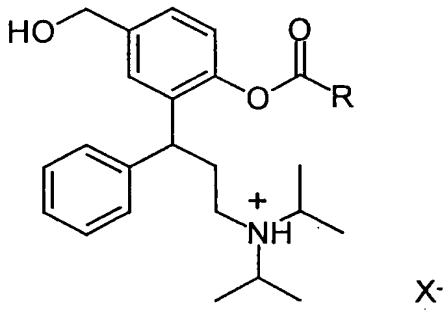
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

4. Verbindungen nach Anspruch 3, dadurch gekennzeichnet, daß X^- jeweils ein Säurerest der Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

5. Verbindungen nach Ansprüchen 3 und 4, dadurch gekennzeichnet, daß sie *R*-(+)-2-(3-(Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobuttersäureester-hydrogenfumarat, *R*-(+)-2-(3-(Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobuttersäureesterhydrochloridhydrat sind.

6. Verbindungen nach Ansprüchen 1 bis 5 in Form eines Schüttgutes.

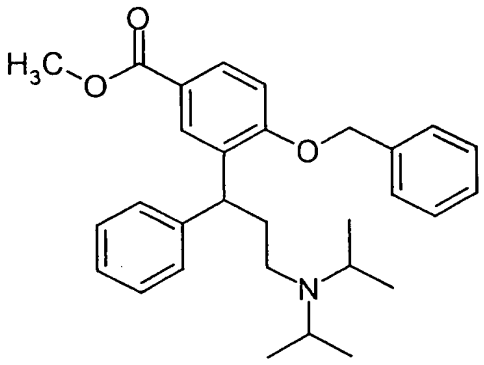
7. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel I



Formel I

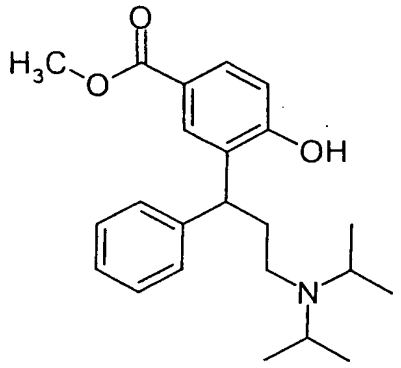
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, dadurch gekennzeichnet, daß

a) eine Verbindung der Formel III



Formel III

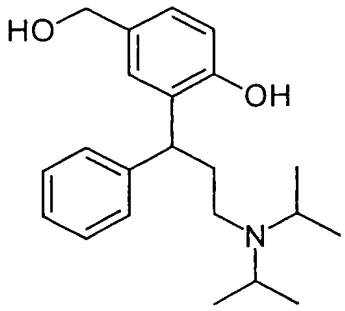
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel V



Formel V

gespalten wird, worauf

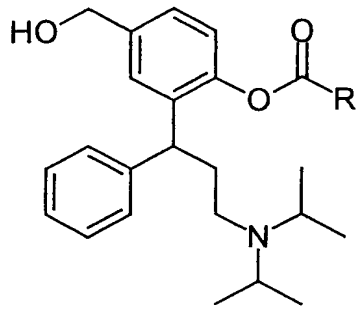
b) die so erhaltene Verbindung der Formel V mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel VI



Formel VI

zu ergeben, die

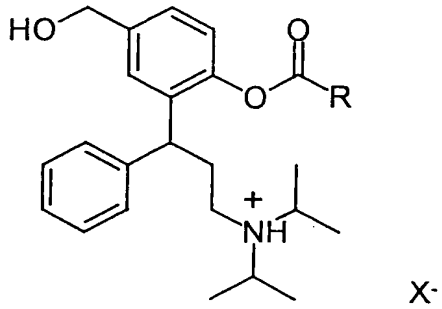
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel A



Formel A

zu erhalten, worin R die oben genannte Bedeutung hat, die

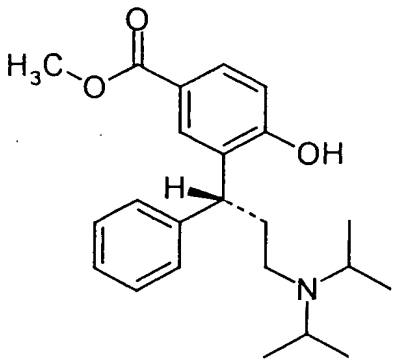
d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel I



Formel I

umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

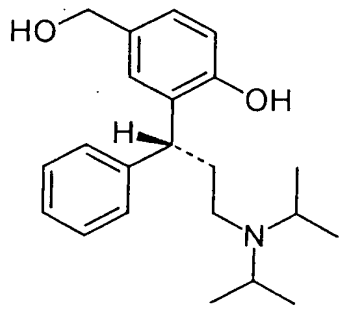
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel 5



Formel 5

gespalten wird, worauf

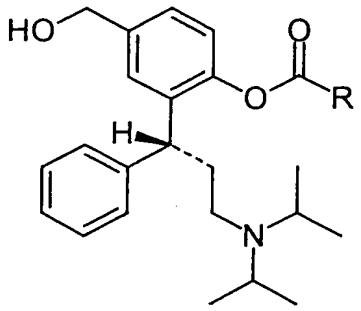
b) die so erhaltene Verbindung der Formel 5 mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel 6



Formel 6

zu ergeben, die

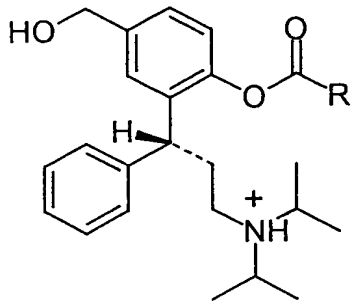
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel 1



Formel 1

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel 2



Formel 2

umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß zur Herstellung der Verbindungen der allgemeinen Formel 2 die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure) Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet werden.

11. Verfahren nach Ansprüchen 7 bis 10, dadurch gekennzeichnet, daß als Hydrierungsmittel vorzugsweise Raney-Nickel/H_2 in Methanol als Lösungsmittel verwendet wird.

12. Verfahren nach Ansprüchen 7 bis 10, dadurch gekennzeichnet, daß als Reduktionsmittel $NaBH_4$/EtOH, vorzugsweise $LiAlH_4$/THF verwendet werden.

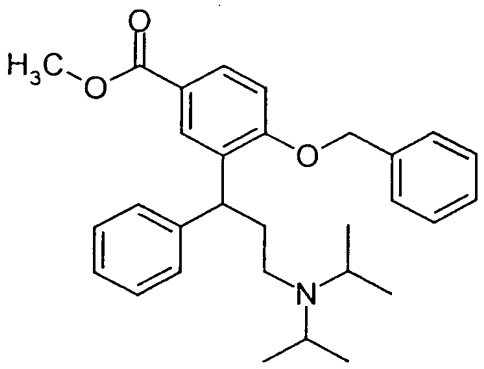
13. Verfahren nach Ansprüchen 7 bis 10, dadurch gekennzeichnet, daß als Acylierungsmittel Isobutyrylchlorid und als Base Triethylamin verwendet werden.

14. Verfahren nach Ansprüchen 9 bis 13, dadurch gekennzeichnet, daß eine Verbindung der Formel 6 mit einem Äquivalent Isobutyrylchlorid in Gegenwart von Triethylamin unter Verwendung eines der jeweiligen Lösungsmittel Ethylacetat, Dichlormethan, Tetrahydrofuran, Acetonitril oder Toluol regio- und chemoselektiv zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester umgesetzt wird.

15. Verfahren nach Ansprüchen 9 bis 14, dadurch gekennzeichnet, daß *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester und Fumarsäure oder Salzsäure unter Bildung des jeweiligen Salzes umgesetzt werden.

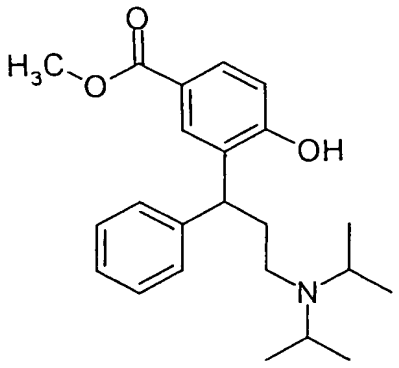
16. Verfahren nach Ansprüchen 9 bis 12 zur Herstellung von R-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat, dadurch gekennzeichnet, daß die phenolische Veresterung von R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) ohne Zusatz einer externen Base durchgeführt wird, indem Lösungen von (6) in Lösungen von Isobuttersäurechlorid, die mindestens 1 Moläquivalent Wasser enthalten, zugetropft werden, um direkt ein entsprechendes stabiles, hydrathaltiges Hydrochlorid zu erhalten.

17. Verbindung der Formel III



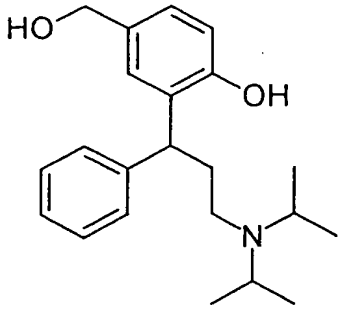
Formel III

18. Verbindung der Formel V



Formel V

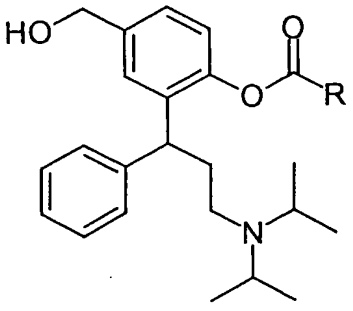
19. Verbindung der Formel VI



Formel VI

20. Verwendung einer Verbindung nach Ansprüchen 17 bis 19 als hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

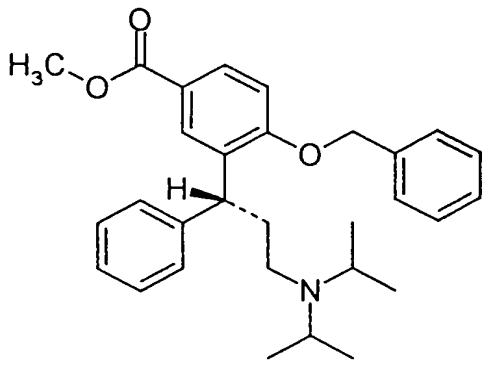
21. Verwendung einer Verbindung nach Ansprüchen 17 bis 19 als Zwischenprodukt bei der Herstellung von phenolischen Monoestern der allgemeinen Formel A



Formel A

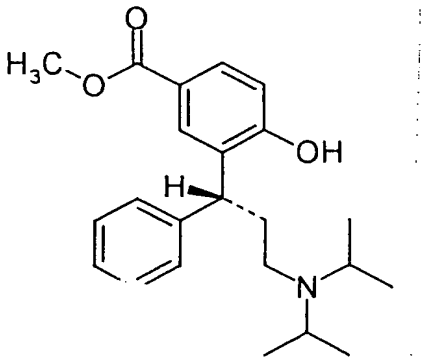
in der R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht.

22. Verbindung der Formel 3



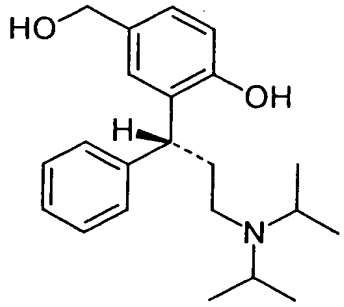
Formel 3

23. Verbindung der Formel 5



Formel 5

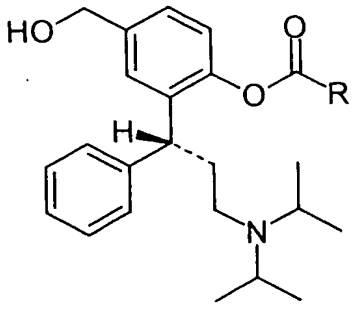
24. Verbindung der Formel 6



Formel 6

25. Verwendung einer Verbindung nach Ansprüchen 22 bis 24 als hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

26. Verwendung einer Verbindung nach Ansprüchen 22 bis 24 als Zwischenprodukt bei der Herstellung von phenolischen Monoestern der allgemeinen Formel 1



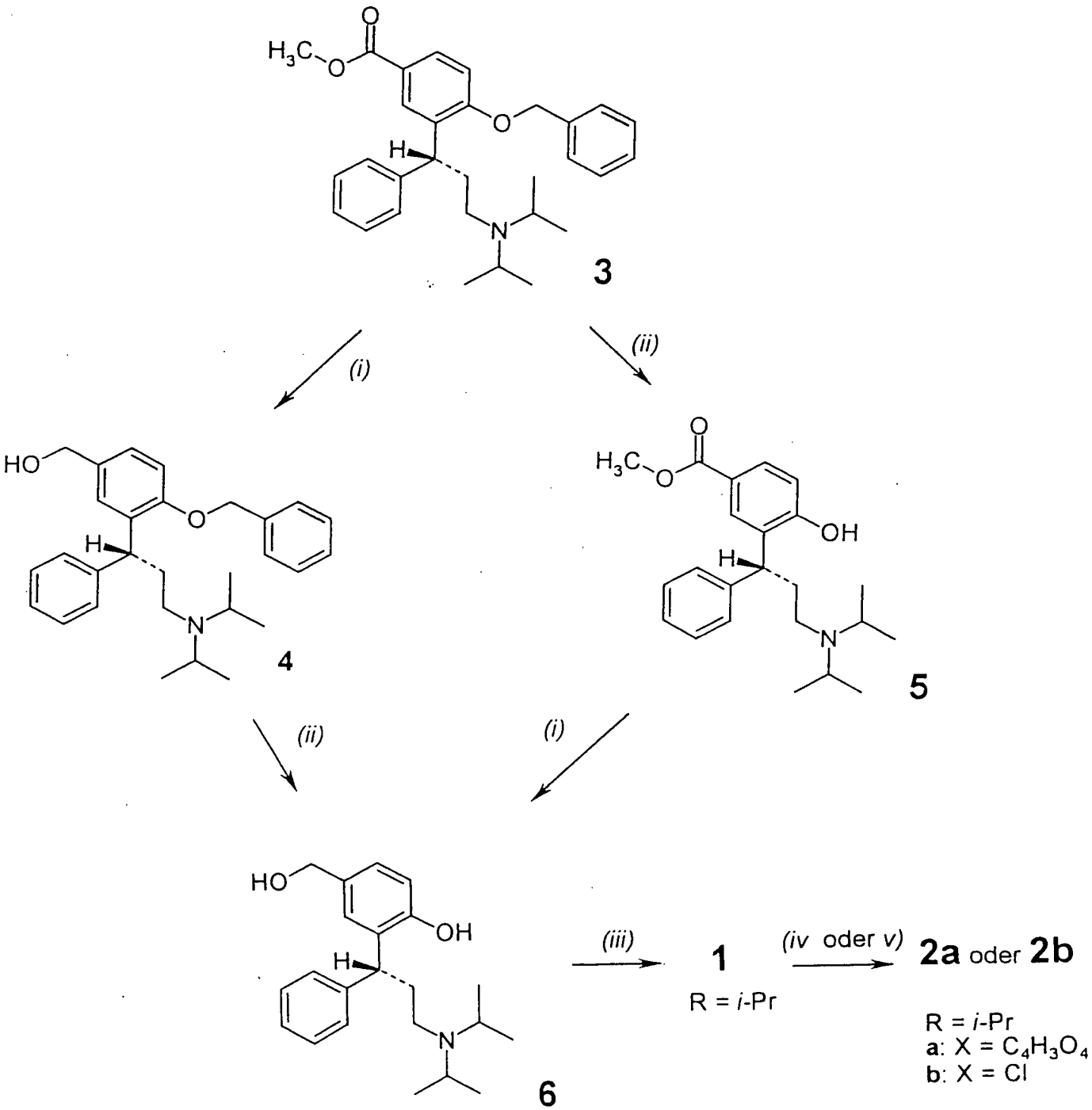
Formel 1

27. Verwendung einer Verbindung nach den Ansprüchen 22 bis 24 als Zwischenprodukt bei der Herstellung von Salzen phenolischer Monoester der allgemeinen Formel 2, in der R die gleiche Bedeutung hat, wie sie in Anspruch 3 angegeben ist.

28. Verwendung einer Verbindung nach den Ansprüchen 22 bis 24 als Zwischenprodukt bei der Herstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

Reaktionsschema 1 1/1

(i), (ii), (iii), (iv), (v) stehen für: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-COCl, Et_3N, (iv), Fumarsäure, (v), Salzsäure; R steht für Isopropyl (iPr)



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Veröffentlicht:
— *Mit internationalem Recherchenbericht.*
— *Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

(54) **Bezeichnung:** STABILE SALZE NEUARTIGER DERIVATE VON 3,3-DIPHENYLPROPYLAMINEN

(57) **Abstract:** The invention relates to highly pure, crystalline, stable compounds of 3,3-diphenylpropylamine derivatives, in the form of their salts, a method for their production and highly pure, stable, intermediate products. The method is particularly characterized by regio- and chemo-selectivity and high yields and provides salts of phenolic monoesters of 3,3-diphenylpropylamines, which are particularly suitable for application in technical pharmaceutic formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrogenfumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrochloride hydrate. The method further provides essential, stable, crystalline intermediate products for the production of the above salts. A preferred intermediate product is *R*-(-)-3-(3-diisopropylaminophenylpropyl)-4-hydroxybenzoic acid methyl ester.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft hochreine, kristalline, stabile Verbindungen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze, Verfahren zu deren Herstellung sowie hochreine, stabile Zwischenprodukte. Insbesondere zeichnet sich das Verfahren durch Regio- und Chemoselektivität sowie hohe Ausbeute aus. Es werden Salze phenolischer Monoester von 3,3-Diphenylpropylaminen zur Verfügung gestellt, die sich besonders gut zum Einsatz in pharmazeutisch-technischen Formulierungen eignen. Bevorzugte Verbindungen sind *R*-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat. Weiterhin werden stabile, kristalline verfahrenswesentliche Zwischenprodukte zum Erhalt der vorgenannten Salze zur Verfügung gestellt. Ein bevorzugtes Zwischenprodukt ist *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester.

WO 01/35957 A1

BESCHREIBUNG

Stabile Salze neuartiger Derivate von 3,3-Diphenylpropylaminen

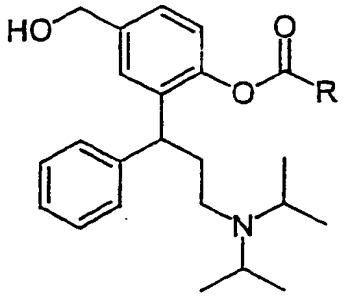
Die vorliegende Erfindung betrifft hochreine, kristalline, stabile Verbindungen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze, Verfahren zu deren Herstellung sowie hochreine, stabile Zwischenprodukte.

Aus dem Dokument PCT/EP99/03212 sind neuartige Derivate von 3,3-Diphenylpropylaminen bekannt.

Sie sind wertvolle Prodrugs [illegible] on Harndrang-Inkontinenz und anderen spas[illegible]'en Nachteil bisher zur Verfügung stehende[illegible] zu geringe Absorption der Wirkstoffe dur[illegible]nen oder deren ungünstigen Metabolismus [illegible]

Weiterhin zeichnen sich diese neuartigen Prodrugs durch verbesserte pharmakokinetische Eigenschaften im Vergleich zu Oxybutynin und Tolterodin aus.

Bevorzugte Verbindungen aus der Gruppe dieser neuartigen Derivate von 3,3-Diphenylpropylaminen sind Ester aliphatischer oder aromatischer Carbonsäuren mit der nachfolgend genannten allgemeinen Formel A



Formel A

in der R die Bedeutung von C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl oder unsubstituiertem oder substituiertem Phenyl hat. Sie können in Form ihrer optischen Isomere, als Racematengemisch und in Form ihrer individuellen Enantiomere vorliegen.

Verbindungen der Struktur der Formel A besitzen allerdings eine geringe Wasserlöslichkeit. Diese verringert ihre orale Bioverfügbarkeit.

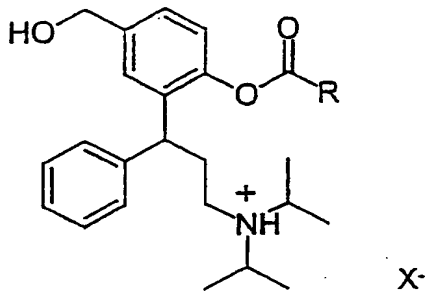
Schließlich neigen Monoester der Struktur, wie sie in Formel A wiedergegeben sind, zu intermolekularer Umesterung.

Bei längerer Lagerung ist deshalb unter Gehaltsabnahme von Verbindungen der Struktur der allgemeinen Formel A eine Zunahme von Diester und freiem Diol feststellbar.

Zwar lassen sich grundsätzlich Salze der Verbindungen der allgemeinen Formel A erhalten, indem Lösungen der Verbindungen der Formel A (Basenteil) mit Lösungen von Säuren in jeweils geeigneten Lösungsmitteln vereinigt werden, jedoch erweisen sich die als Festkörper erhaltenen Salze als durchweg amorph und/oder hygroskopisch und sind auch aus den üblichen Lösungsmitteln nicht ohne weiteres kristallisierbar. Derartige Salze weisen eine zu geringe chemische Stabilität auf, um als wertvolle pharmazeutische Wirkstoffe galenisch verarbeitet werden zu können.

Überraschenderweise wurde nun gefunden, daß sich die vorgenannten Nachteile vermeiden lassen, wenn Verbindungen der Struktur der allgemeinen Formel A, nachdem sie unter spezieller Reaktionsführung dargestellt wurden, mit einer physiologisch verträglichen anorganischen oder organischen Säure der allgemeinen Formel H-X, in der ^-X den jeweiligen Säurerest

bedeutet, zu ihrem jeweiligen Salz der allgemeinen Formel I umgesetzt werden.



Formel I

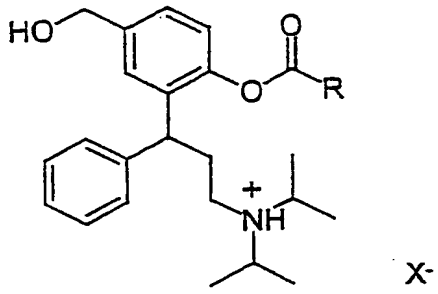
Es ist daher Aufgabe der vorliegenden Erfindung, hochreine, kristalline, stabile Verbindugen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze zur Verfügung zu stellen, die die erwähnten Nachteile vermeiden und sich besonders gut zum Einsatz in pharmazeutisch-technischen Formulierungen eignen und zu solchen verarbeiten lassen.

Eine weitere Aufgabe der vorliegenden Erfindung ist es, ein Verfahren zur Herstellung derartiger hochreiner, kristalliner, stabiler Verbindungen in Form ihrer Salze sowie hochreine, kristalline, stabile Zwischenprodukte zur Verfügung zu stellen.

Schließlich ist es Aufgabe der Erfindung, ein Verfahren zur Herstellung der vorgenannten Verbindungen zur Verfügung zu stellen, mit dem die Verfahrensprodukte und die jeweiligen Zwischenprodukte chemo- und regioselektiv in hoher Ausbeute erhalten werden.

Diese Aufgabe wurde dadurch gelöst, daß hochreine, kristalline, stabile Verbindungen der 3,3-Diphenylpropylamine in Form

ihrer Salze der allgemeinen Formel I zur Verfügung gestellt werden,



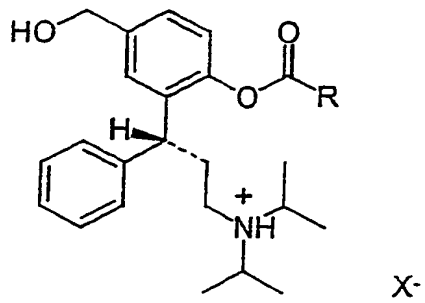
Formel I

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

Nach einer Ausführung der Erfindung können die Salze der allgemeinen Formel I den jeweiligen Säurerest X^- der nachfolgend genannten Säuren enthalten:

Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure.

Nach einer weiteren Ausführungsform der Erfindung werden *R*-konfigurierte Verbindungen der allgemeinen Formel 2 zur Verfügung gestellt,



Formel 2

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

Nach einer vorteilhaften Ausführungsform der Erfindung können die Verbindungen in Form ihrer Salze der allgemeinen Formel 2 den jeweiligen Säurerest X^- der nachfolgend genannten Säuren enthalten:

Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin),

Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

Bevorzugte Verbindungen der vorliegenden Erfindung sind die Salze

- *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat

und

- *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

Weiterhin sind solche Verbindungen bevorzugt, worin R für Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, 4-(1-Cyclopropyl-methanoyloxy)-phenyl, 4-(1-Cyclobutyl-methanoyloxy)-phenyl, 4-(1-Cyclohexyl-methanoyloxy)-phenyl oder 4-(2,2-Dimethyl-propanoyloxy)-phenyl steht und X^- Chlorid bedeutet.

Bevorzugt sind insbesondere [(R)-3-(2-{1-[4-(1-Cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenylpropyl]-diisopropyl-ammoniumchlorid, [(R)-3-(2-{1-[4-(1-Cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammoniumchlorid, [(R)-3-(2-{1-[4-(1-Cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammoniumchlorid, [(R)-3-(2-{1-[4-(2,2-Dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammoniumchlorid, {(R)-3-[2-(1-Cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammoniumchlorid, {(R)-3-[2-(1-Cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-

ammoniumchlorid, {(R)-3-[2-(1-Cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium-chlorid, {(R)-3-[2-(1-Cyclohexyl-methanoyloxy)-5-hydroxy-methyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammoniumchlorid.

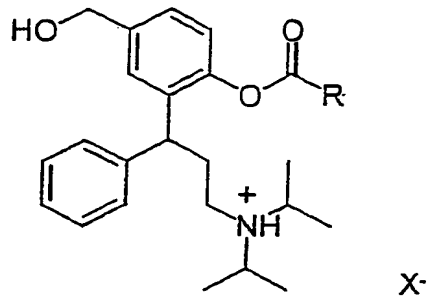
In den Verbindungen der vorliegenden Erfindung bedeutet der Ausdruck „alkyl" vorzugsweise eine geradkettige oder verzweigtkettige Kohlenwasserstoffgruppe mit 1 bis 6 C-Atomen. Besonders bevorzugt sind Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl. Der Ausdruck „Cycloalkyl" bezeichnet zyklische Kohlenwasserstoffgruppen, die 3 bis 10 Kohlenstoffatome aufweisen, die auch geeignete Substituenten anstelle der Wasserstoffatome enthalten können.

Der Ausdruck „Phenyl" bezeichnet eine $-C_6H_5$-Gruppe, die substituiert oder unsubstituiert sein kann. Geeignete Substituenten können beispielsweise Alkyl, Alkoxy, Halogen, Nitro und Amin sein. Der Ausdruck „Alkoxy" hat, bezogen auf den Alkylteil, die gleiche Bedeutung, wie sie bereits oben für „alkyl" angegeben wurde. Geeignete Halogene sind Fluor-, Chlor-, Brom- und Iodatome.

Die vorliegende Erfindung umfaßt auch Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel I sowie wertvoller Zwischenprodukte.

Das Verfahren zeichnet sich durch Chemo- und Regioselektivität sowie hohe Ausbeute aus.

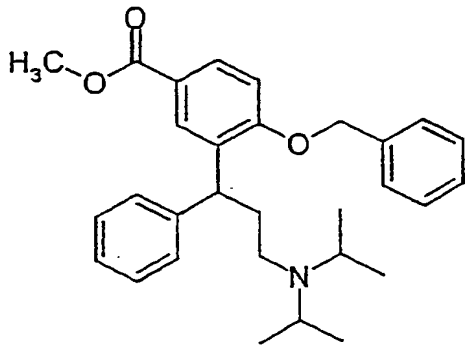
Verbindungen der allgemeinen Formel I



Formel I

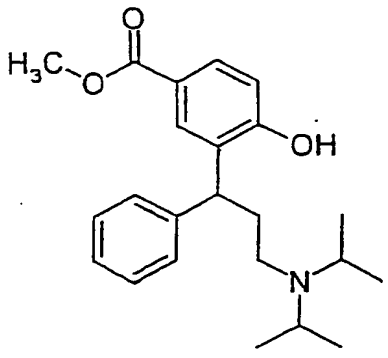
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, werden hergestellt, indem

a) eine Verbindung der Formel III



Formel III

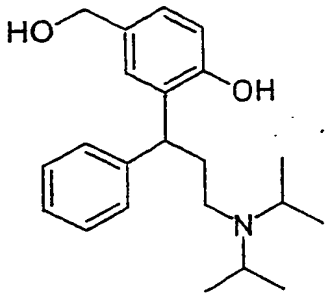
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel V



Formel V

gespalten wird, worauf

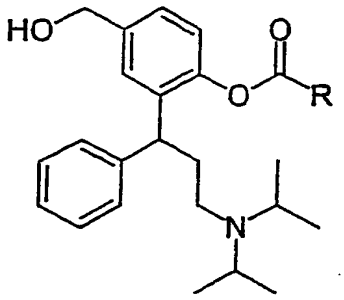
b) die so erhaltene Verbindung der Formel V mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel VI



Formel VI

zu ergeben, die

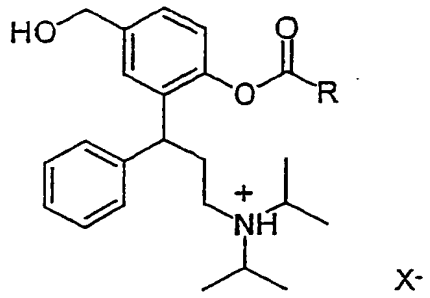
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel A



Formel A

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel I

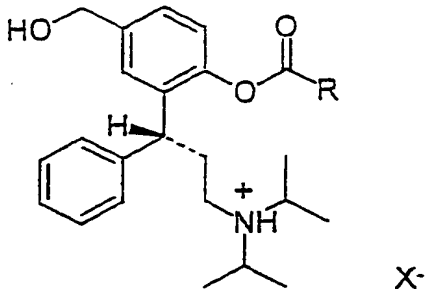


Formel I

umgesetzt wird, worin R für C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

Verfahrensgemäß werden zur Herstellung der Verbindungen der allgemeinen Formel I die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoylglycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet.

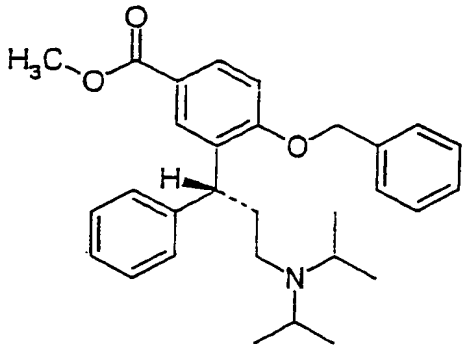
Nach einer vorteilhaften Weiterbildung der Erfindung wird ein Verfahren zur Herstellung von *R*-konfigurierten Verbindungen der allgemeinen Formel 2 beschrieben,



Formel 2

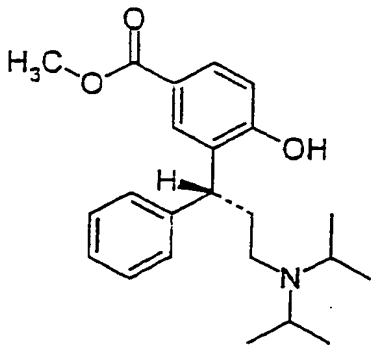
worin R für C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, indem

a) eine Verbindung der Formel 3



Formel 3

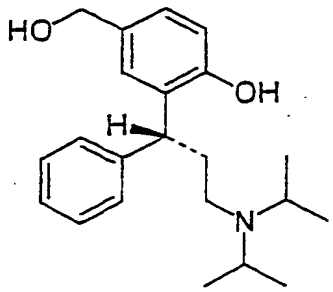
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel 5



Formel 5

gespalten wird, worauf

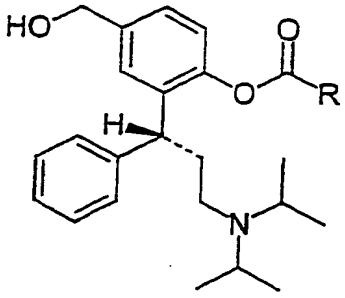
b) die so erhaltene Verbindung der Formel 5 mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel 6



Formel 6

zu ergeben, die

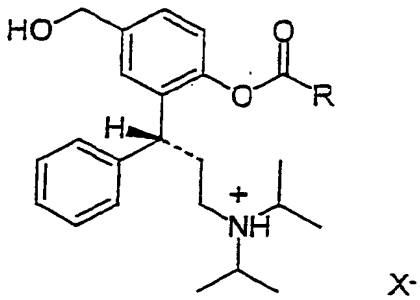
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel 1



Formel 1

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel 2



Formel 2

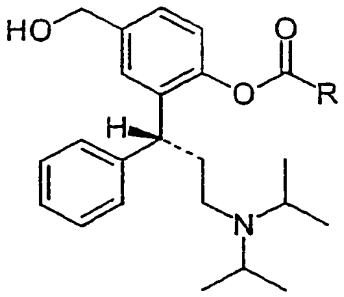
umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

Vorteilhafterweise werden zum Erhalt von Verbindungen der allgemeinen Formel 2 verfahrensgemäß die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet.

Besonders vorteilhaft wird, ausgehend von dem kristallinen *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)benzoesäuremethylester, das hochreine, kristalline Zwischenprodukt

R-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester dargestellt, das zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol reduziert wird, schließlich geeignet acyliert wird und anschließend mit einer physiologisch verträglichen anorganischen oder organischen Säure unter spontaner Kristallisation zum jeweiligen hochreinen, kristallinen, stabilen Salz umgesetzt wird.

Je nach verwendetem Säurechlorid werden Verbindungen der allgemeinen Formel 1 erhalten,



Formel 1

in der R die Bedeutung von C_1-C_6-alkyl, insbesondere Isopropyl, C_3-C_{10}-cycloalkyl oder unsubstituiertem oder substituiertem Phenyl hat.

Zum Erhalt der erfindungsgemäßen Verbindungen in Form ihrer Salze ist die spezielle Reaktionsführung über besondere Zwischenstufen und individualisierbare Zwischenprodukte entscheidend.

Dies wird anhand des Reaktionsschemas 1 (siehe Figur 1) erläutert, in dem Umsetzungen mit *R*-konfigurierten Verbindungen, ohne darauf beschränkt zu sein, beschrieben werden.

Darin bedeuten:

3 = *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure- methylester

4 = *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5 = *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester

6 = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1 = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester

2a = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl-isobuttersäureester Hydrogenfumarat

2b = *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester Hydrochlorid Hydrat

Entsprechend der in den Ausführungsbeispielen erläuterten Reaktionsführung wird die Vorstufe 3 (*R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure-methylester) kristallin und rein dargestellt.

Vorstufe 3 wird nach üblichen Methoden - z.B. BBr_3, $AlCl_3$ - vorzugsweise jedoch mittels Wasserstoffgas über Raney-Nickel in Methanol als Lösungsmittel bei Raumtemperatur (RT) zu 5 (*R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester) gespalten. Dieses fällt in hochreiner, kristalliner Form (Schmp. 143.7 °C) an.

Schließlich wird 5 mit einem geeigneten Reduktionsmittel - z.B. $NaBH_4$/EtOH - vorzugsweise $LiAlH_4$ in einem inerten Lösungsmittel bei niedrigen Temperaturen (-78°C bis + 10°C) reduziert und die Verbindung 6 (*R*-(+)-2-(3-Diisopropylamino-

1-phenylpropyl)-4-hydroxymethylphenol) erhalten. Die Verbindung 6 wird hochrein erhalten und kann aus einem geeigneten Lösungsmittel, wie beispielsweise Ethylacetat, kristallisiert werden. Das farblose feinkristalline Material besitzt einen Schmelzpunkt von 102.3°C. Dies ist insofern überraschend, als die Verbindung 6 im Stand der Technik als amorpher Festkörper beschrieben wird.

Verbindung 6 wird nun in sehr guter Ausbeute und Regio- und Chemoselektivität, zu einem phenolischen Ester acyliert. Diese Reaktion wird bei RT oder niedrigen Temperaturen mit einem Äquivalent Säurechlorid in Gegenwart einer Base in geeigneten Lösungsmitteln ausgeführt. Geeignete Lösungsmittel sind Ethylacetat, Dichlormethan, Tetrahydrofuran, Acetonitril oder Toluol.

Bevorzugt wird die Reaktion mit Isobutyrylchlorid als Säurechlorid und Triethylamin als Base bei den oben angegebenen Temperaturen durchgeführt. Das dann erhaltene 1 (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester) fällt in so hoher Reinheit an, daß mit Lösungen der Fumarsäure in geeigneten Lösungsmitteln spontane Kristallisation unter Bildung des Hydrogenfumarat-Salzes 2a einsetzt.

Dieses Salz zeigt einen scharfen Schmelzpunkt von 103°C, ist bei RT stabil, nicht hygroskopisch und schließt kein Kristallösemittel ein. Es läßt sich beliebig oft umkristallisieren.

Wird anstatt Fumarsäure wasserfreie Salzsäure - z.B. als etherische Lösung - verwendet, tritt ebenfalls Salzbildung unter Erhalt des kristallinen Produktes 2b (*R*-(+)-2-(3-

Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobuttersäureester Hydrochlorid Hydrat ein.

Nach erneuter Umkristallisation weist das Produkt 2b einen Schmelzpunktsbereich von 97 - 106°C auf.

Schließlich kann das Produkt 2b ganz besonders vorteilhaft durch die folgende Variante der inversen Reaktionsführung, ausgehend von der Verbindung 6 des Reaktionsschemas 1 direkt erhalten werden. Das Produkt 2b ist damit ohne Zusatz einer externen säure-fangenden Base erhältlich, wie nachfolgend erläutert wird.

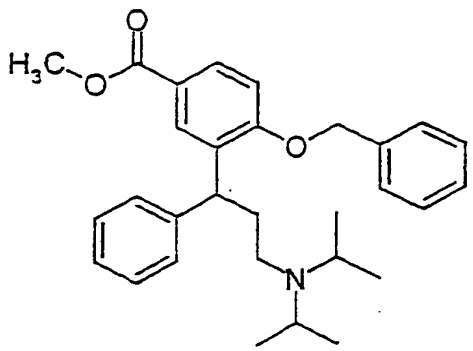
Lösungen von 6 (*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) werden in Lösungen von Isobuttersäurechlorid getropft, so daß unter geeigneten Polaritätsbedingungen rasch das wasserfreie Produkt 2b auskristallisiert. 2b ist sehr hygroskopisch.

Wird die vorgenannte Reaktion in feuchten Lösungsmitteln durchgeführt, die mindestens ein Moläquivalent Wasser enthalten, wird direkt ein stabiles und kristallines, hydrathaltiges Produkt 2b erhalten, das die oben genannten Schmelzeigenschaften aufweist.

Die erfindungsgemäßen Verbindungen der allgemeinen Formeln I und 2 eignen sich als Schüttgut.

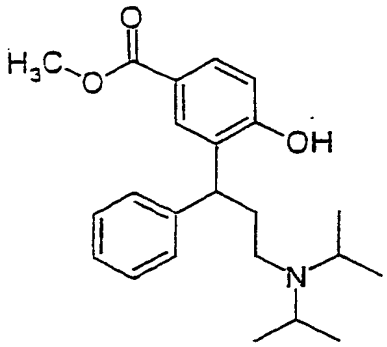
Besonders vorteilhaft sind die hochrein erhältlichen Verbindungen der allgemeinen Formeln III, V, VI, 3, 5, 6 und 7.

Verbindung der Formel III



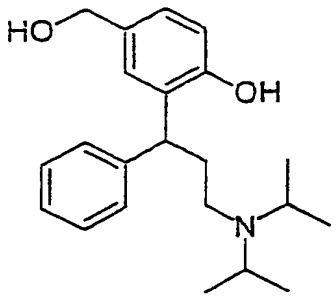
Formel III

Verbindung der Formel V



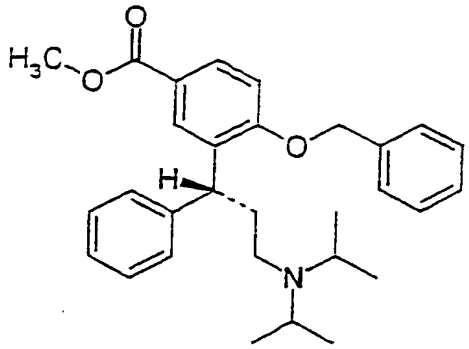
Formel V

Verbindung der Formel VI



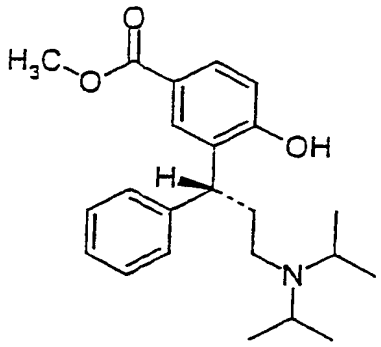
Formel VI

Verbindung der Formel 3



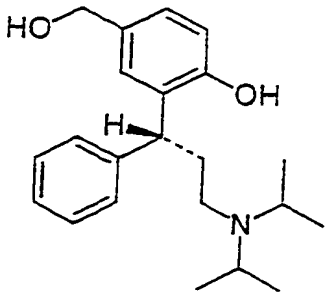
Formel 3

Verbindung der Formel 5



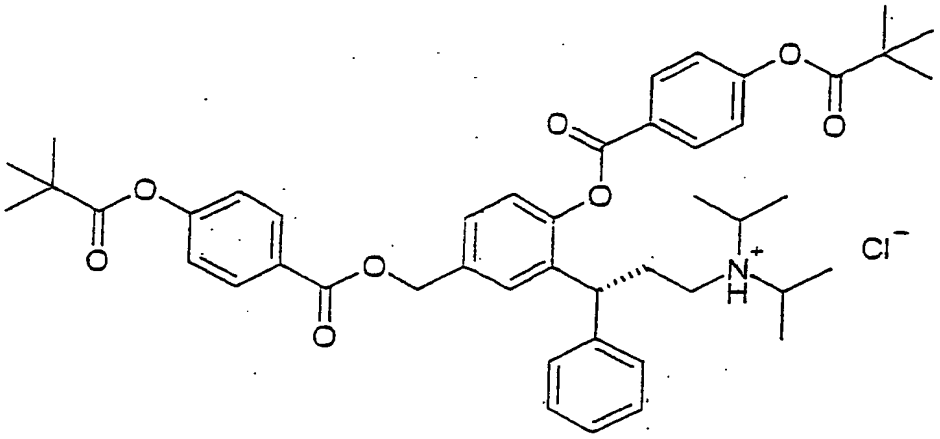
Formel 5

Verbindung der Formel 6



Formel 6

Verbindung der Formel 7



Formel 7

[(R)-3-(2-{1-[4-(2,2-Dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chlorid

Die vorgenannten Verbindungen III, V, VI, 3, 5, 6 und 7 eignen sich besonders zur Verwendung als jeweils hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

Besonders vorteilhaft eignen sich diese Verbindungen zur Verwendung als Zwischenprodukt bei der Herstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

Schließlich kann das Verfahren besonders vorteilhaft ausgeführt werden, indem eine Verbindung der allgemeinen Formel 6 (siehe Reaktionsschema 1) mit einem Äquivalent Isobutyrylchlorid in Gegenwart von Triethylamin unter Verwendung eines der jeweiligen Lösungsmittel Ethylacetat, Dichlormethan, Te-

trahydrofuran, Acetonitril oder Toluol regio- und chemoselektiv zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester umgesetzt wird.

Verfahrensgemäß eignet sich besonders vorteilhaft *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester zur Umsetzung mit Fumarsäure oder Salzsäure unter Bildung des jeweiligen Salzes.

Die nachfolgenden Ausführungsbeispiele erläutern die Erfindung.

Experimentelles

I. Allgemeines

Alle Verbindungen wurden vollständig durch ^{1}H und ^{13}C NMR-Spektroskopie charakterisiert (Bruker DPX 200). Die angeführten chemischen Verschiebungen in den ^{13}C-NMR-Spektren (50 MHz, ppm Werte aufgeführt) beziehen sich auf die Lösungsmittelresonanzen von $CDCl_3$ (77.10 ppm). ^{1}H NMR Daten ($CDCl_3$; 200 MHz, ppm) beziehen sich auf internes Tetramethylsilan).

Dünnschichtchromatographie (DC, R_f angegeben) wurde durchgeführt auf 5x10 cm E. Merck Kieselgelfolien (60F254), die Flecken wurden visualisiert durch Fluoreszenzlöschung oder Ansprühen mit alkalischer Kaliumpermanganatlösung.

Laufmittelsysteme waren: (1), n-Hexan / Aceton / Triethylamin (70/20/10, v/v-%); (2), Toluol / Aceton / Methanol / Essigsäure (70/5/20/5, v/v-%).

Die optischen Drehungen wurden bei einer Wellenlänge von 589.3 nm (Natrium D-Linie) vermessen, bei Raumtemperatur unter Verwendung des Lösungsmittels Ethanol (Gerät: Perkin Elmer Polarimeter Type 241),

Schmelzpunkte (Schmp., in °C) sind unkorrigiert und wurden am Gerät Mettler FP 1 bestimmt, bzw. Differentialthermoanalyse (DSC) am Perkin Elmer Modell DSC7, Auswertungssoftware „Pyris".

UV/VIS-Messungen wurden am Spektrophotometer Modell Lambda 7 (Perkin-Elmer) bei einer Schichtdicke von 1 cm durchgeführt. Angegeben ist die spezifische Absorption einer 1-%igen Lösung ($A^{1\%}_{1\,cm}$).

IR-Spektren wurden an einem Perkin-Elmer FTIR Spektrometer Serie 1610 aufgezeichnet (Auflösung 4 cm^{-1}).

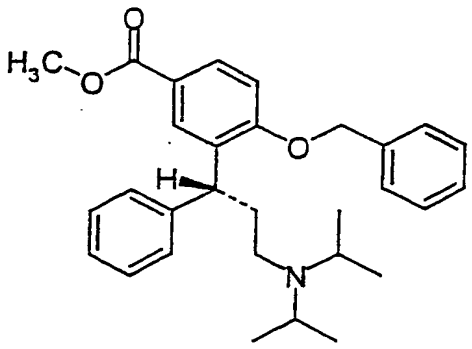
Gaschromatographie-Massenspektrometrie (GC-MS, m/z-Werte und relative Intensität bezogen auf das Basision (%)) wurde mit einem Finnigan TSQ 700 Triple Mass Spectrometer im positiv (P-CI) oder negativ (N-CI) chemische Ionisationsmeßbetrieb mit Methan oder Ammoniak als Reaktantgas bzw. über Elektronenstoßionisation aufgenommen. Hydroxyverbindungen wurden als Trimethylsilylether-Derivate vermessen.

Gekoppelte Flüssigkeitschromatographie-Massenspektrometrie (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z-Werte und relative Intensität (%) werden über einen Massenbereich von 50-500 a.m.u. angegeben.

II. Ausführungsbeispiele

Die in Klammern gesetzten arabischen Zahlen (3), (4), (5), (6) beziehen sich auf die identischen Bezeichnungen im Reaktionsschema 1.

1. Darstellung von
R-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäuremethylester (3)



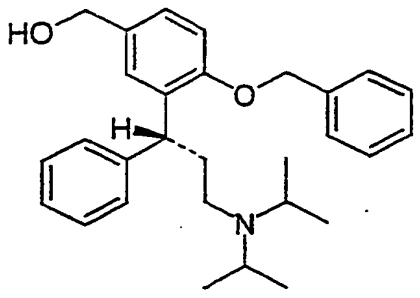
Eine Lösung von *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäure Hydrochlorid (2.30 kg, 4.77 Mol) in 26.4 Liter Methanol und 0.25 Liter konzentrierter Schwefelsäure wird 16 Stunden unter Rückfluß erhitzt. Anschließend wird ein Drittel des Lösungsmittels abdestilliert, abgekühlt und unter Rühren mit 5 kg Eis und 2.5 Liter 25%-iger wässriger Kaliumcarbonatlösung versetzt. Der Ansatz wird erst mit 15 Liter, dann nochmals mit 5 Liter Dichlormethan extrahiert. Die organischen Phasen werden vereinigt und am Rotationsverdampfer zur Trockene eingeengt. Man erhält 1.99 kg (90.7 % der Theorie) hellgelbes Öl in ca. 90 % Reinheit (DC, NMR).
DC (1): 0.58

^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.83, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22, 129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Umkristallisation

69.0 g öliges Rohprodukt werden in 150 ml siedendem Methanol gelöst. Nach dem Zusatz von 15 ml destilliertem Wasser wird bei 0°C belassen, wobei sich farblose Kristalle abscheiden. Diese werden abfiltriert, mit wenig kaltem Methanol gewaschen und im Vakuum getrocknet. Ausbeute: 41.8 g (60.6 % der Theorie) farblose Kristalle, Schmp. 89.8 °C; $[I]_D^{20}$ = - 30.7 (c = 1.0, Ethanol).

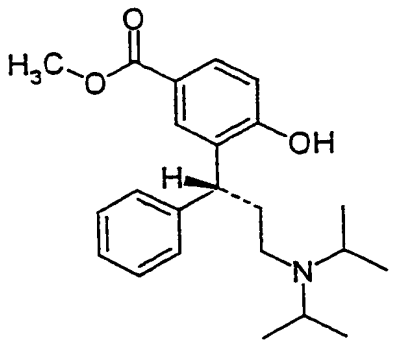
2. Darstellung von
R-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)



Rohprodukt (3) (28 g) wird in 230 ml absolutem Diethylether gelöst und unter Rühren in eine Suspension von 1.8 g Lithiumaluminiumhydrid in Diethylether (140 ml) getropft. Nach 18 Stunden Rühren bei Raumtemperatur werden tropfenweise 4.7 ml Wasser zugesetzt. Die organische Phase wird abgetrennt, mit

wasserfreiem Natriumsulfat getrocknet, filtriert und am Rotationsverdampfer zur Trockene eingeengt. Man erhält 26 g (98.9 % der Theorie) *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) als farbloses Öl.
DC (2): 0.32; $[I]_D^{20}$ = + 6.3 (c = 1.0, Ethanol).
^{13}C-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.

3. Darstellung von
R-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester (5)



Zu einer gerührten Suspension von 5 g Raney-Nickel (mit Wasser, dann mit Methanol gewaschen) in 200 ml Methanol werden 10 g (21.8 mmol) *R*-(-)-4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoesäuremethylester (3) zugesetzt. Nach kurzem Erwärmen, um alles (3) vollständig zu lösen, wird die Apparatur unter eine Atmosphäre von Wasserstoffgas gesetzt. Nach drei Stunden Rühren bei Normaldruck und Raumtemperatur zeigt die Dünnschichtchromatographie vollständige Umsetzung. Der Ansatz wird mit Stickstoffgas gespült und nach Zusatz von etwas Aktivkohle filtriert. Nach dem Einengen der methanolischen Lösung am Rotationsverdampfer

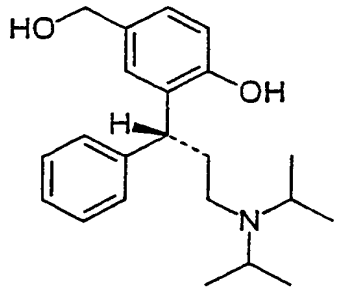
verbleiben 6.0 g (75 % der Theorie) *R*-(-)-3-(3-Diisopropyl-aminophenyl-propyl)-4-hydroxy-benzoesäuremethylester (5) in Form farbloser Kristalle in einer Reinheit von 99.6 % (HPLC).

Schmp. 143.7 °C; DSC 144.7°C

$[I]_D^{20}$ = - 26.6 (c = 0.93, Ethanol).

^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Darstellung von
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol (6)



a) Ausgehend von der Zwischenstufe (4), *R*-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) werden in 220 ml Methanol gelöst und mit Raney-Nickel (5 g) versetzt. Die Apparatur wird mit Wasserstoffgas gespült und der Ansatz zwei Tage bei Raumtemperatur gerührt. Nach dem Zusatz von weiteren 5 g Raney-Nickel wird zwei weitere Tage bei Raumtemperatur unter Wasserstoffgasatmosphäre gerührt, vom Katalysator abfiltriert und das Filtrat am Rotationsverdampfer zur Trockene eingeengt. Der ölige, blaßgelbe Rückstand wird in 100 ml

Diethylether gelöst, zweimal mit je 100 ml Wasser gewaschen, über Natriumsulfat getrocknet, filtriert und zur Trockene eingeengt. Man erhält 14.1 g (90.4 % der Theorie) *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol in Form eines cremefarbenen, amorphen Festkörpers. Umkristallisation siehe unten c).

b) Ausgehend von der Zwischenstufe (5); *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester

Eine Lösung von 370 mg (1.0 mmol) *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester in 20 ml wasserfreiem Tetrahydrofuran wird langsam und bei Raumtemperatur zu einer gerührten Mischung von trockenem Tetrahydrofuran (10 ml) und einer 1M Lösung von Lithiumaluminiumhydrid in Tetrahydrofuran (3 ml) (unter Stickstoffschutzgasatmosphäre) getropft. Überschüssiges Hydrid wird durch tropfenweisen Zusatz einer gesättigten Natriumcarbonatlösung zersetzt. Nach dem Abtrennen der organischen Phase wird diese am Rotationsverdampfer eingeengt und anschließend im Hochvakuum getrocknet. Es werden 274 mg (74 % der Theorie) blaßgelbes Öl erhalten, das sich langsam zu einer amorphen Masse verfestigt.

c) Umkristallisation:

Rohprodukt 6 (1.0 g) wird in Ethylacetat gelöst und am Rotationsverdampfer erneut eingeengt. Das so von Fremdlösemitteln (Diethylether bzw. Tetrahydrofuran, s.o.) befreite Diol wird unter leichtem Erwärmen mit 1.5 ml Ethylacetat versetzt. Man rührt, bis eine klare Lösung entstanden ist, läßt auf Raumtemperatur abkühlen und setzt einige Impfkristalle zu. Letztere werden gewonnen, indem rohes 6 über HPLC gereinigt wird,

die Hauptfraktion aufgefangen wird, eingeengt und der Rückstand mehrere Stunden im Hochvakuum getrocknet wird. Nachdem deutliche Kristallisation eingetreten ist, beläßt man bei - 10 °C. Die Kristalle werden noch in der Kälte abgesaugt und im Vakuum getrocknet. Man erhält farblose Kristalle in 84 % Ausbeute.

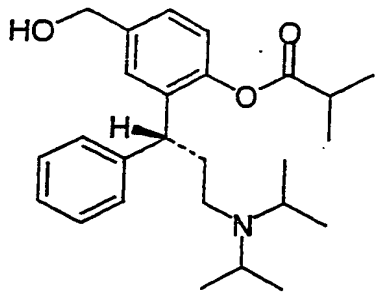
Schmp. 102.3 °C

DC (1): 0.57

$[I]_D^{20}$ = + 21.3 (c = 1.0, Ethanol).

^{13}C-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.

5. Darstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester (1)



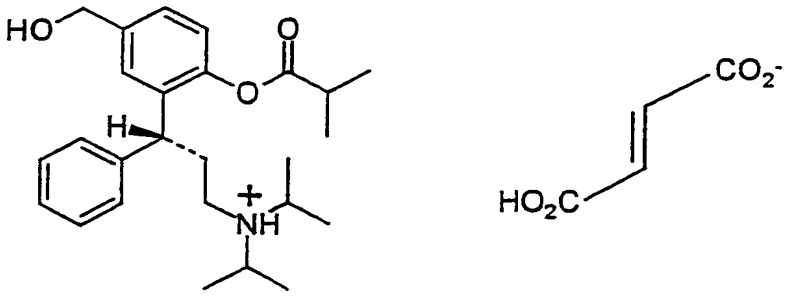
Eine Lösung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) und Triethylamin (20.4 g, 201.7 mmol) in 750 ml Dichlormethan wird unter Rühren und Kühlung (-5 °C) mit einer Lösung von Isobutter-

säurechlorid (23.4 g, 201.7 mmol) in 250 ml Dichlormethan versetzt. Nach der Zugabe wird noch 15 Min. bei 0 °C, dann 30 Min. bei Raumtemperatur gerührt und nacheinander mit Wasser (250 ml) und 5%-iger wässriger Natriumhydrogencarbonat-Lösung gewaschen. Die organische Phase wird abgetrennt und am Rotationsverdampfer zur Trockene eingeengt. Der Ester *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester wird als farbloses, viskoses Öl erhalten; Ausbeute: 77.1 g (98.4 % der Theorie).

DC (1): 0.26; $[I]_D^{22}$ = + 2.7 (c = 1.0, Ethanol).

^{13}C-NMR ($CDCl_3$):19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125.59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Darstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat



Eine Lösung von 41.87 g (102 mmol) *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester in 90 ml 2-Butanon wird unter Erwärmen mit Fumarsäure (11.81 g, 102 mmol) versetzt. Nach dem Lösen der Säure wird

langsam unter Rühren Cyclohexan (20-30 ml) bis zum Einsetzen einer Trübung zugesetzt. Man beläßt den farblosen, homogenen Ansatz zunächst 18 Stunden bei Raumtemperatur, dann mehrere Stunden bei 0 °C. Die ausgefallenen farblosen Kristalle werden abgesaugt, mit wenig Cyclohexan/2-Butanon (90:10, Vol.-%) gewaschen und im Vakuum bei 30 °C getrocknet. Man erhält 44.6 g (83.1 % der Theorie) des Hydrogenfumarat-Salzes des *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester in Form farbloser Plättchen.

Schmp. 98.8 °C, eine zweite Kristallisation aus dem gleichen Lösungsmittelgemisch ergibt das Produkt mit einem Schmp. von 103 °C.

$[I]_D^{20}$ = + 6.0 (c = 1.0, Ethanol).

Elementaranalyse: Berechnet für $C_{30}H_{41}NO_7$ (Molgewicht 527.66) C 68.29 %, H 7.83 %, N 2.65 %, O 21.2 %; gefunden C 68.29 %, H 7.90 %, N 2.72 %, O 21.0 %.

UV/VIS bei Σ in nm ($A^{1\%}_{1\,cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

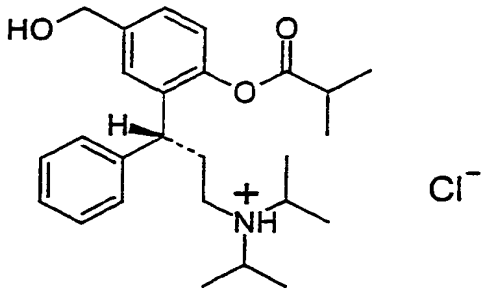
^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 ($\underline{C}H_2OH$); 6.832 (=CH, Fumarat); 6.84-7.62 (Aryl, = CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CH\underline{C}H_2$); 34.09 ($\underline{C}H$-C=O); 41.87 ($CH\underline{C}H_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52,

142.35, 147.54 (Aryl CH); 135.54 (=CH, Fumarat); 170.48 (C=O, Fumarat); 175.62 (i-Pr-C=O).

MS im Direkteinlaß, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Darstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobuttersäureester Hydrochlorid Hydrat



Eine Lösung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester (8.54 g, 25.0 mmol) in 50 ml Dichlormethan wird bei 0°C langsam in eine gerührte Lösung von Isobuttersäurechlorid (2.66 g, 25.0 mmol) in 100 ml Dichlormethan getropft. Nach einer Stunde wird die Kühlung entfernt und noch eine Stunde bei Raumtemperatur nachgerührt. Nach dem Abziehen der flüchtigen Bestandteile im Vakuum am Rotationsverdampfer hinterbleibt ein farbloser, amorph-fester Schaum. Dieser Rückstand wird in Aceton (17 ml) gelöst, mit 0.45 bis 0.50 g Wasser und Diethylether versetzt (ca.20 - 25 ml) bis deutliche Trübung eintritt. Nach kurzer Behandlung mit Ultraschall tritt spontane Kristallisation ein und es

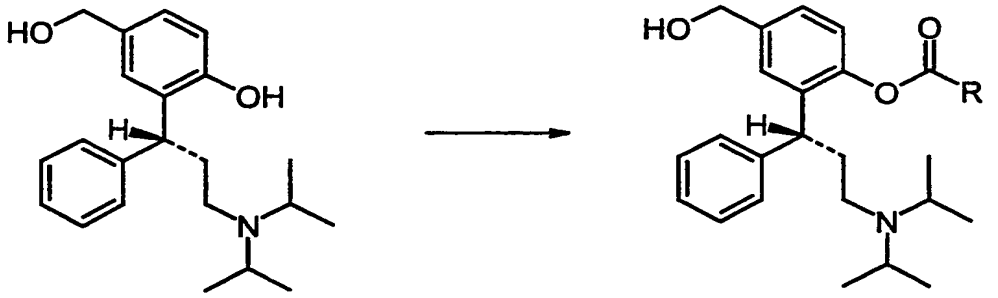
werden unter Rühren langsam weitere 80 ml Diethylether zugetropft. Die ausgefallenen farblosen Kristalle werden abgesaugt und über Nacht im Vakuum über Phosphorpentoxid getrocknet. Man erhält 10.5 g (93.7 % der Theorie) farblos kristallines *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat in 97.0 % Reinheit (HPLC).

Schmp. 97.1 °C.

$[I]_D^{20}$ = + 4.3 (c = 1.03, Ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolische Monoester



Allgemeine Arbeitsvorschrift zur Herstellung von phenolischen Monoestern

In eine Lösung von 120.3 mg (0.352 mmol) R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml Dichlormethan wird unter Rühren bei 0 °C eine Lösung von Säurechlorid (0.352 mmol) in 2 ml Dichlormethan eingetropft. Anschließend wird mit Triethylamin-Dichlormethan (49.1 µl/0.353 mmol-2 ml) versetzt. Nach 18 Stunden bei Raumtemperatur zeigt die Dünnschichtchromatographie vollständige Umsetzung. Der Ansatz wird nacheinander mit 5 ml Wasser, wässriger 0.1N-Salzsäure, 5 ml 5%-iger wässriger Natriumhydrogencarbonatlösung, 5 ml Wasser gewaschen, über Natriumsulfat getrocknet, und nach der Filtration zur Trockene eingeengt. Anschließend wird im Hochvakuum bis zur Gewichtskonstanz getrocknet.

Nach diesem Verfahren wurden folgende Verbindungen beispielhaft hergestellt:

R = $CH_2CH(CH_3)_2$

R-(+)-3-Methylbuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-ester

Farbloses Öl in 70% Ausbeute und >95% Reinheit (NMR).
^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.
DC (1): 0.76.

R = $CH_2C(CH_3)_3$

R-(+)-3,3-Dimethylbuttersäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, freie Base.

Farbloses Öl in 69.7% Ausbeute und >95% Reinheit (NMR).
^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.
DC (1): 0.75.

R = $(CH_3)_3C$

R-(+)-Pivalinsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid.

Farblose Kristalle, Schmp. 165-6 °C.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R = c-C_3H_5

R-(+)-Cyclopropancarbonsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid.

Farblose wachsartige Masse.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35,

129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R = c-C_4H_7

R-(+)-Cyclobutancarbonsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid

Farblose wachsartige Masse.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R = c-C_5H_9

R-(+)-Cyclopentancarbonsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid

Farblose wachsartige Masse.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R = c-C_6H_{11}

R-(+)-Cyclohexancarbonsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid

Farblose wachsartige Masse.
^{13}C-NMR (DMSO-d_6 =39.7 ppm):
174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R = 4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-(Ethylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropyl-amino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
Hydrochlorid

Farblose Kristalle, Schmp. 195-8 °C.
^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H mit D_2O austauschbar, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.0 Hz, 1H, Phenyl-H3), 7.41-7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H mit D_2O austauschbar, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.6 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.97-2.74 (m, 2H, CH_2), 2.67 (q, J = 7.4 Hz, 2H, CH_2), 2.56-2.43 (m, 2H, CH_2), 1.23-1.13 (m, 15H, 2 × CH(C<u>H</u>$_3)_2$, CH_3).

R = 4-(i-$C_3H_7CO_2$)-C_6H_4

R-(+)-4-(Isopropylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester Hydrochlorid

Farblose Kristalle, Schmp. 202-4 °C.

^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H mit D_2O austauschbar, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.4 Hz, 1H, Phenyl-H3), 7.42-7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H mit D_2O austauschbar, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.99-2.78 (m, 3H, CH_2, C<u>H</u>$(CH_3)_2$), 2.54-2.47 (m, 2H, CH_2), 1.29-1.13 (m, 18H, 3 × CH(C<u>H</u>$_3)_2$).

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-(+)-4-(t-Butylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, freie Base.

Farbloses Öl.

^{1}H-NMR (DMSO-d_6): 8.19-8.12 (m, 2H, Phenyl-H), 7.45-7.33 (m, 3H, Phenyl-H), 7.25-7.09 (m, 7H, Phenyl-H), 5.20 (t, J = 5.6 Hz, 1H, OH), 4.50 (d, J = 5.6 Hz, 2H, CH_2), 4.20 (t, J = 7.5 Hz, 1H, CH), 2.95-2.80 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.38-2.25 (m, 2H, CH_2), 2.09-2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82-0.76 (m, 12H, 2 × CH(C<u>H</u>$_3)_2$).

Hydrochlorid: farblose Kristalle, Schmp. 165-6 °C.

^{1}H-NMR ($CDCl_3$): 8.22-8.16 (m, 2H, Phenyl-H), 8.02 (d, J = 1.8 Hz, 1H, Phenyl-H), 7.27-7.02 (m, 9H, Phenyl-H), 4.83-4.60 ('m', 2H, CH_2), 4.01-3.94 (m, 1H, CH), 3.66-3.54 (m, 2H),

3.18-2.80 (m, 3H), 2.53-2.44 (m, 1H) (2 × CH_2, 2 × $C\underline{H}(CH_3)_2$), 1.43-1.25 (m, 21H, $(CH_3)_3$, 2 × $CH(C\underline{H}_3)_2$).

R = 4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(Cyclopropylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester Hydrochlorid

Farblose Kristalle, Schmp. 208-213 °C.

^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H mit D_2O austauschbar, NH), 8.15-8.09 (m, 2H, Phenyl-H), 7.53 ('d', 1H, Phenyl-H3), 7.42-7.13 (m, 9H, Phenyl-H), 5.25 (br s, 1H mit D_2O austauschbar, OH), 4.52 (s, 2H, CH2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.53 (m, 2H, 2 × C<u>H</u>(CH3)2), 3.05-2.70 (m, 2H, CH2), 2.51-2.37 (m, 2H, CH2), 2.01-1.89 (m, 1H, Cyclopropyl-CH), 1.20-1.05 (m, 16H, 2 × CH(C<u>H</u>3)2, 2 × Cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6 = 39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R = 4-(c-$C_4H_7CO_2$)-C_6H_4

R-(+)-4-(Cyclobutylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester Hydrochlorid

Farblose Kristalle, Schmp. 201-6 °C.

^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H mit D_2O austauschbar, NH), 8.17-8.12 (m, 2H, Phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, Phenyl-H3),

7.42-7.14 (m, 9H, Phenyl-H), 5.25 (br s, 1H mit D_2O austauschbar, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.47 (m, 3H, Cyclobutyl-CH), 2 × $C\underline{H}(CH_3)_2$), 3.00-2.70 (m, 2H, CH_2), 2.51-2.26 (m, 6H, CH_2, 2 × Cyclobutyl-CH_2), 2.10-1.85 (m, 2H, Cyclobutyl-CH_2), 1.22-1.12 (m, 12H, 2 × $CH(C\underline{H}_3)_2$).

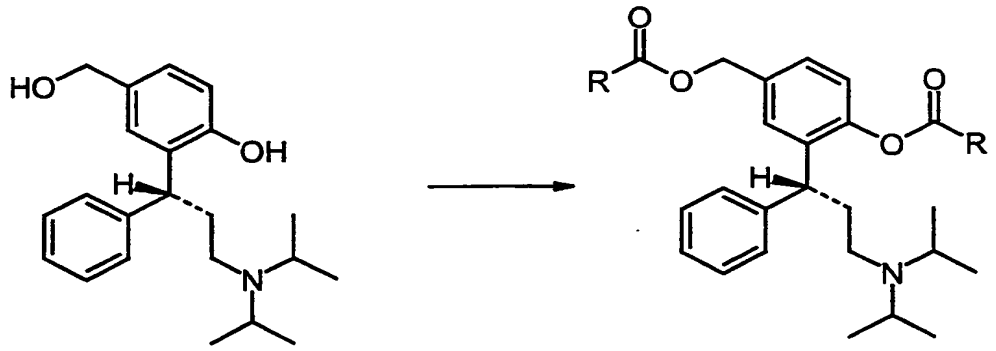
R = 4-(c-$C_6H_{11}CO_2$)-C_6H_4

R-(+)-4-(Cyclohexylcarbonyloxy)-benzoesäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester Hydrochlorid

Farblose Kristalle, Schmp. 212-217 °C.

^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, *mit D_2O austauschbar*, NH), 8.16-8.12 (m, 2H, Phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, Phenyl-H3), 7.39-7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, *mit D_2O austauschbar*, OH), 4.53 (d, J = 4.2 Hz, 2H, CH_2), 4.22 (t, J = 7.5 Hz, 1H, CH), 3.62-3.48 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 3.00-2.60 (m, 3H, Cyclohexyl-CH), CH_2), 2.51-2.40 (m, 2H, CH_2), 2.07-1.98 (m, 2H, Cyclohexyl-CH_2), 1.80-1.11 (m, 20H, 4 × Cyclohexyl-CH_2), 2 × $CH(C\underline{H}_3)_2$)

9. Identische Diester



Allgemeine Arbeitsvorschrift zur Herstellung von identischen Diestern

In eine Lösung von 7.30 g (21.4 mmol) R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml Dichlormethan wird unter Rühren bei 0 °C eine Lösung von Säurechlorid (49.2 mmol) in 50 ml Dichlormethan eingetropft. Anschließend wird mit Triethylamin-Dichlormethan (6.86 ml/ 49.2 mmol-50 ml) versetzt. Nach 1-3 Stunden bei Raumtemperatur zeigt die Dünnschichtchromatographie vollständige Umsetzung. Der Ansatz wird nacheinander mit jeweils 100 ml Wasser, wässriger 0.1N-Salzsäure, 5 ml 5%-iger wässriger Natriumhydrogencarbonatlösung, 5 ml Wasser gewaschen, über Natriumsulfat getrocknet, und nach der Filtration zur Trockene eingeengt. Anschließend wird im Hochvakuum bis zur Gewichtskonstanz getrocknet.

Nach diesem Verfahren wurden folgende Verbindungen beispielhaft hergestellt:

R = Methyl

R-(-)-Essigsäuresäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, freie Base

Blaßgelbes Öl, Reinheit (HPLC): 95.2%.
^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.
LC-MS: 425 (15%, $M^{+\cdot}$), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).
$[\alpha]_D^{20}$ = -33.1 (c = 1, CH_3CN).
DC (1): 0.79.

R = Cyclohexyl

R-Cyclohexancarbonsäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Blaßgelbes Öl, Reinheit (NMR): >95%.
^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.
DC (1): 0.96.

R = Isopropyl

R-Isobuttersäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Freie Base: blaßgelbes Öl, Reinheit (HPLC): 95.6%.

^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.

DC (1): 0.74.

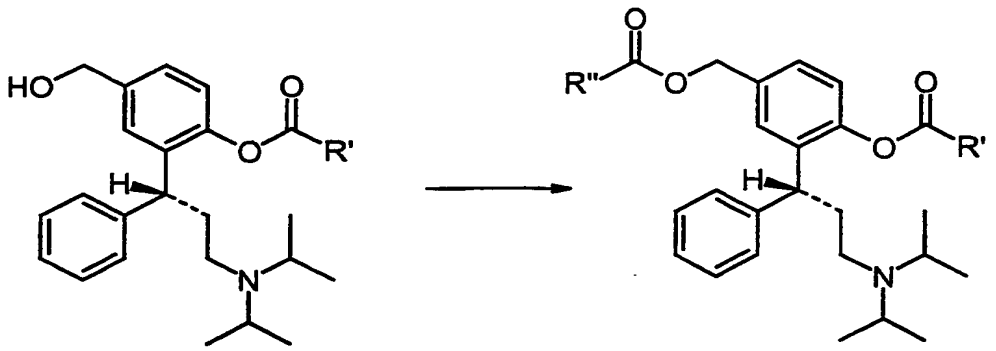
Hydrogenfumarat-Salz: farbloser Sirup, 94.4% HPLC-Reinheit.
^{13}C-NMR ($CDCl_3$): 17.89,
18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-4-(t-Butylcarbonyloxy)-benzoesäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoesäure)-phenyl-ester Hydrochlorid

Farblose Kristalle, Schmp. 105-7 °C.
^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Gemischte Diester



R' ist ungleich R"

Allgemeine Arbeitsvorschrift zur Herstellung von gemischten Diestern

In eine Lösung von 5.30 mmol phenolischen Monoester der allgemeinen Formel A in 40 ml Dichlormethan wird unter Rühren bei 0 °C eine Lösung von Säurechlorid (5.83 mmol) in 15 ml Dichlormethan eingetropft. Anschließend wird mit Triethylamin-Dichlormethan (0.589g/5.82 mmol-15 ml) versetzt. Nach 18 Stunden bei Raumtemperatur zeigt die Dünnschichtchromatographie vollständige Umsetzung. Der Ansatz wird nacheinander mit jeweils 50 ml Wasser, wässriger 0.1N-Salzsäure, 5 ml 5%-iger wässriger Natriumhydrogencarbonatlösung, 5 ml Wasser gewaschen, über Natriumsulfat getrocknet, und nach der Filtration zur Trockene eingeengt. Anschließend wird im Hochvakuum bis zur Gewichtskonstanz getrocknet.

Nach diesem Verfahren wurden folgendes Beispiel hergestellt:

R' = $CH(CH_3)_2$

R'' = CH_3

R-Isobuttersäure-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Farbloses Öl.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

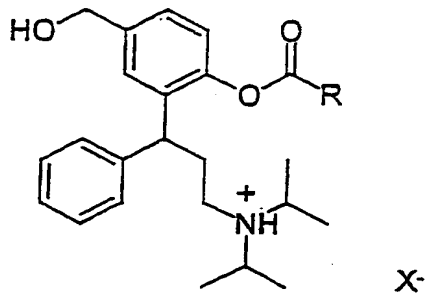
Hydrochlorid: farblose Kristalle

^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$ = +14.6 (c = 1, $CHCl_3$).

PATENTANSPRÜCHE

1. Verbindungen der allgemeinen Formel I



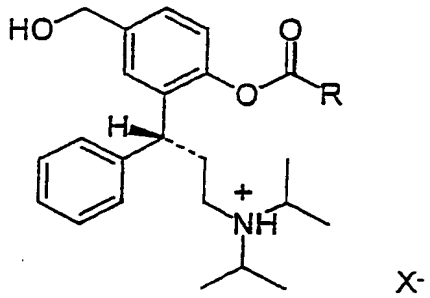
Formel I

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

2. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß X^- jeweils ein Säurerest der Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydro-

xybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

3. Verbindungen nach Ansprüchen 1 und 2, dadurch gekennzeichnet, daß sie die allgemeine Formel 2 besitzen,



Formel 2

worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- der Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure ist.

4. Verbindungen nach Anspruch 3, dadurch gekennzeichnet, daß X^- jeweils ein Säurerest der Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure,

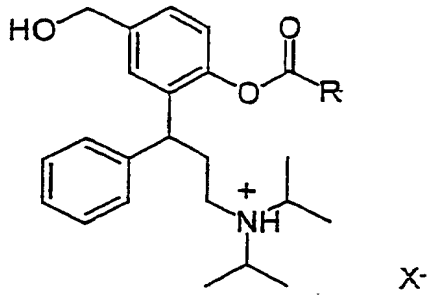
L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure), Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder der Orotsäure ist.

5. Verbindungen nach Ansprüchen 3 und 4, dadurch gekennzeichnet, daß sie *R*-(+)-2-(3-(Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobuttersäureesterhydrogenfumarat, *R*-(+)-2-(3-(Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureesterhydrochloridhydrat sind.

6. Verbindungen nach Ansprüchen 3 und 4, dadurch gekennzeichnet, daß R für Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, 4-(1-Cyclopropyl-methanoyloxy)-phenyl, 4-(1-Cyclobutyl-methanoyloxy)-phenyl, 4-(1-Cyclohexyl-methanoyloxy)-phenyl oder 4-(2,2-Dimethyl-propanoyloxy)-phenyl steht und X^- Chlorid bedeutet.

7. Verbindungen nach Ansprüchen 1 bis 6 in Form eines Schüttgutes.

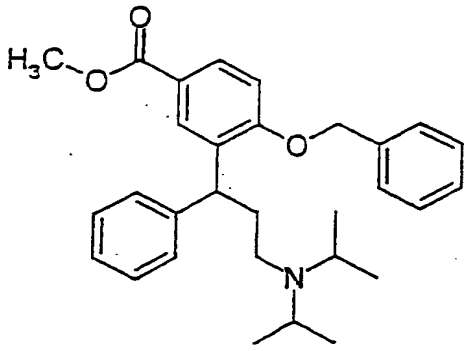
8. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel I



Formel I

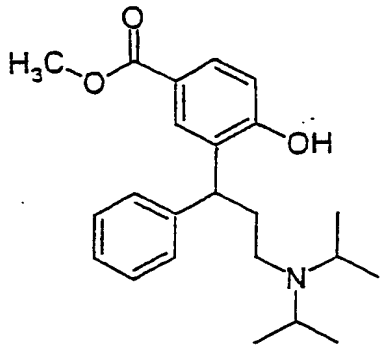
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, dadurch gekennzeichnet, daß

a) eine Verbindung der Formel III



Formel III

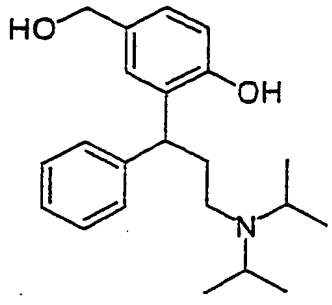
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel V



Formel V

gespalten wird, worauf

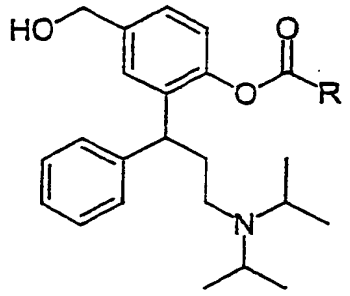
b) die so erhaltene Verbindung der Formel V mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel VI



Formel VI

zu ergeben, die

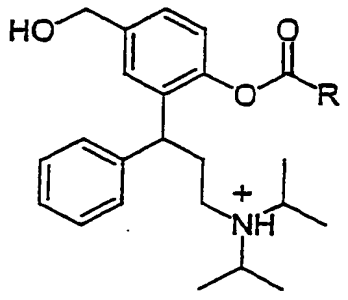
c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel A



Formel A

zu erhalten, worin R die oben genannte Bedeutung hat, die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel I

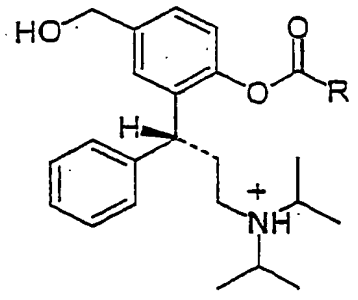


Formel I

umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß zur Herstellung der Verbindungen der allgemeinen Formel I die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenzschleimsäure) Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet werden.

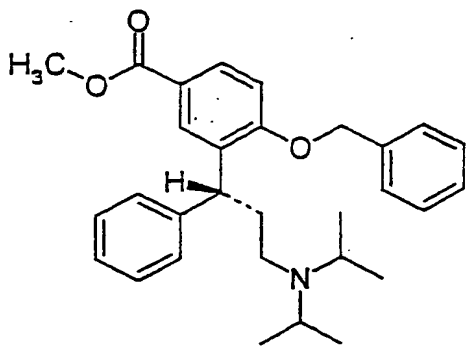
10. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel 2



Formel 2

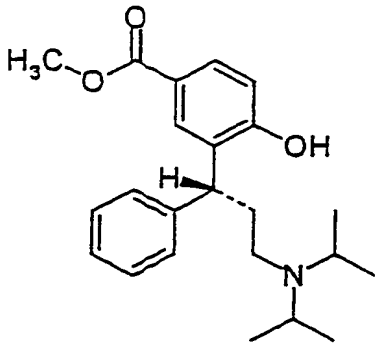
worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht, dadurch gekennzeichnet, daß

a) eine Verbindung der Formel 3



Formel 3

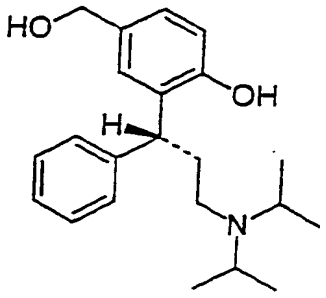
mit einem Hydrierungsmittel zur Bildung einer Verbindung der Formel 5



Formel 5

gespalten wird, worauf

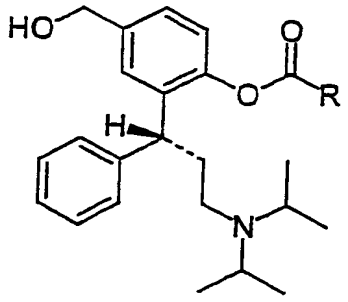
b) die so erhaltene Verbindung der Formel 5 mit einem Reduktionsmittel umgesetzt wird, um eine Verbindung der Formel 6



Formel 6

zu ergeben, die

c) mit einem Acylierungsmittel umgesetzt wird, um eine Verbindung der Formel 1

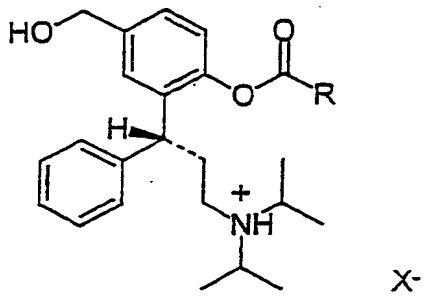


Formel 1

zu erhalten, worin R die oben genannte Bedeutung hat,

die

d) mit einer physiologisch verträglichen anorganischen oder organischen Säure unter Bildung einer Verbindung der Formel 2



Formel 2

umgesetzt wird, worin R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituiertes oder substituiertes Phenyl steht und X^- für den Säurerest einer physiologisch verträglichen anorganischen oder organischen Säure steht.

11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß zur Herstellung der Verbindungen der allgemeinen Formel 2 die Säuren Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Schwefelsäure, Salpetersäure, Essigsäure, Propionsäure, Palmitinsäure, Stearinsäure, Maleinsäure, Fumarsäure, Oxalsäure, Bernsteinsäure, DL-Äpfelsäure, L-(-)-Äpfelsäure, D-(+)-Äpfelsäure, DL-Weinsäure, L-(+)-Weinsäure, D-(-)-Weinsäure, Citronensäure, L-Asparaginsäure, L-(+)-Ascorbinsäure, D-(+)-Glucuronsäure, 2-Oxopropionsäure (Brenztraubensäure), Furan-2-carbonsäure (Brenz-

schleimsäure) Benzoesäure, 4-Hydroxybenzoesäure, Salicylsäure, Vanillinsäure, 4-Hydroxyzimtsäure, Gallussäure, Hippursäure (N-Benzoyl-glycin), Acetursäure (N-Acetylglycin), Phloretinsäure (3-(4-Hydroxyphenyl)-propionsäure), Phthalsäure, Methansulphonsäure oder Orotsäure verwendet werden.

12. Verfahren nach Ansprüchen 8 bis 11, dadurch gekennzeichnet, daß als Hydrierungsmittel vorzugsweise Raney-Nickel/H_2 in Methanol als Lösungsmittel verwendet wird.

13. Verfahren nach Ansprüchen 8 bis 11, dadurch gekennzeichnet, daß als Reduktionsmittel $NaBH_4$/EtOH, vorzugsweise $LiAlH_4$/THF verwendet werden.

14. Verfahren nach Ansprüchen 8 bis 11, dadurch gekennzeichnet, daß als Acylierungsmittel Isobutyrylchlorid und als Base Triethylamin verwendet werden.

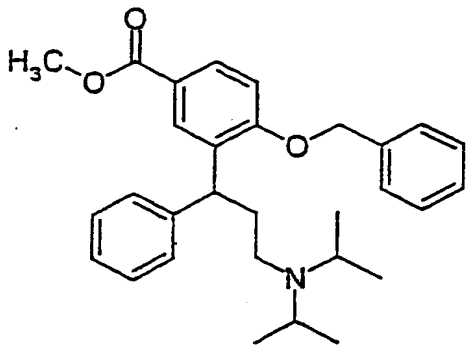
15. Verfahren nach Ansprüchen 10 bis 14, dadurch gekennzeichnet, daß eine Verbindung der Formel 6 mit einem Äquivalent Isobutyrylchlorid in Gegenwart von Triethylamin unter Verwendung eines der jeweiligen Lösungsmittel Ethylacetat, Dichlormethan, Tetrahydrofuran, Acetonitril oder Toluol regio- und chemoselektiv zu *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester umgesetzt wird.

16. Verfahren nach Ansprüchen 10 bis 15, dadurch gekennzeichnet, daß *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester und Fumarsäure oder Salzsäure unter Bildung des jeweiligen Salzes umge-

setzt werden.

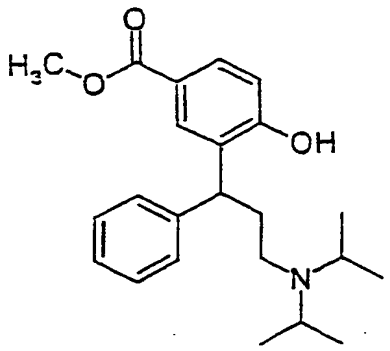
17. Verfahren nach Ansprüchen 10 bis 13 zur Herstellung von R-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat, dadurch gekennzeichnet, daß die phenolische Veresterung von R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) ohne Zusatz einer externen Base durchgeführt wird, indem Lösungen von (6) in Lösungen von Isobuttersäurechlorid, die mindestens 1 Moläquivalent Wasser enthalten, zugetropft werden, um direkt ein entsprechendes stabiles, hydrathaltiges Hydrochlorid zu erhalten.

18. Verbindung der Formel III



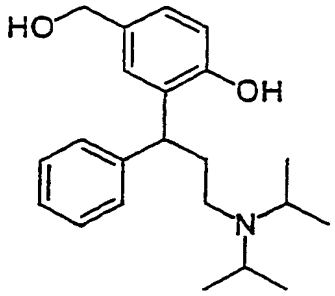
Formel III

19. Verbindung der Formel V



Formel V

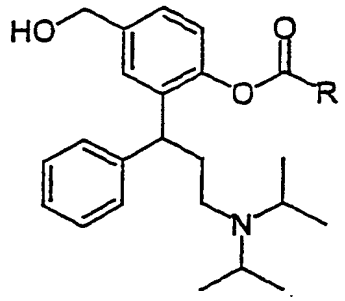
20. Verbindung der Formel VI



Formel VI

21. Verwendung einer Verbindung nach Ansprüchen 18 bis 20 als hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

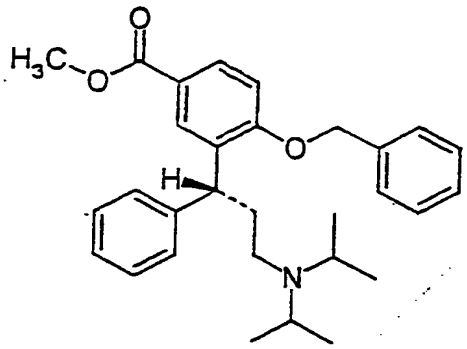
22. Verwendung einer Verbindung nach Ansprüchen 18 bis 20 als Zwischenprodukt bei der Herstellung von phenolischen Monoestern der allgemeinen Formel A



Formel A

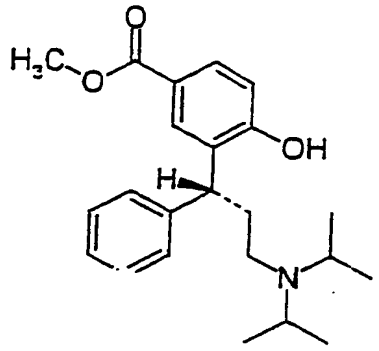
in der R für C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituiertes oder unsubstituiertes Phenyl steht.

23. Verbindung der Formel 3



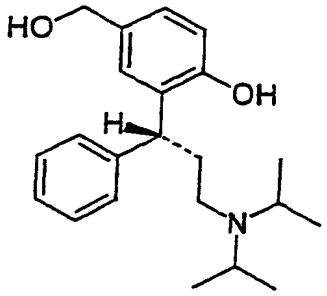
Formel 3

24. Verbindung der Formel 5



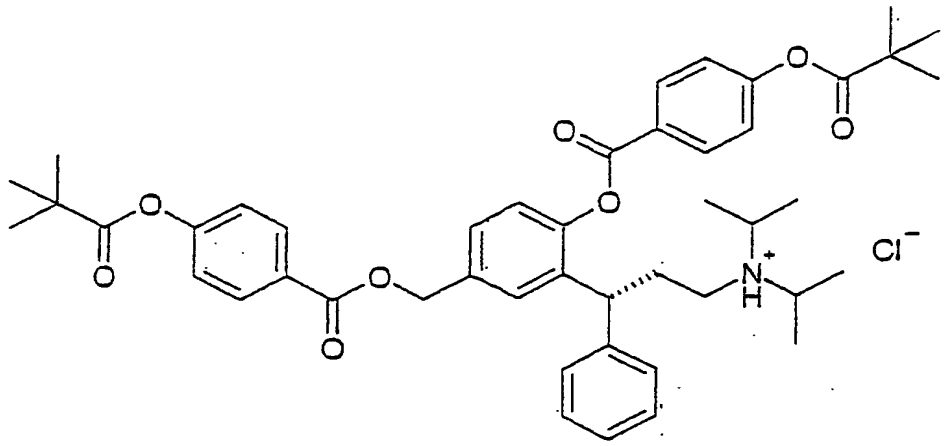
Formel 5

25. Verbindung der Formel 6



Formel 6

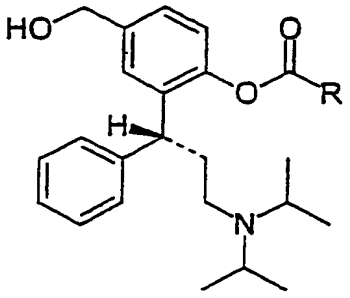
26. Verbindung der Formel 7



Formel 7

27. Verwendung einer Verbindung nach Ansprüchen 23 bis 26 als hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen.

28. Verwendung einer Verbindung nach Ansprüchen 23 bis 26 als Zwischenprodukt bei der Herstellung von phenolischen Monoestern der allgemeinen Formel 1



Formel 1

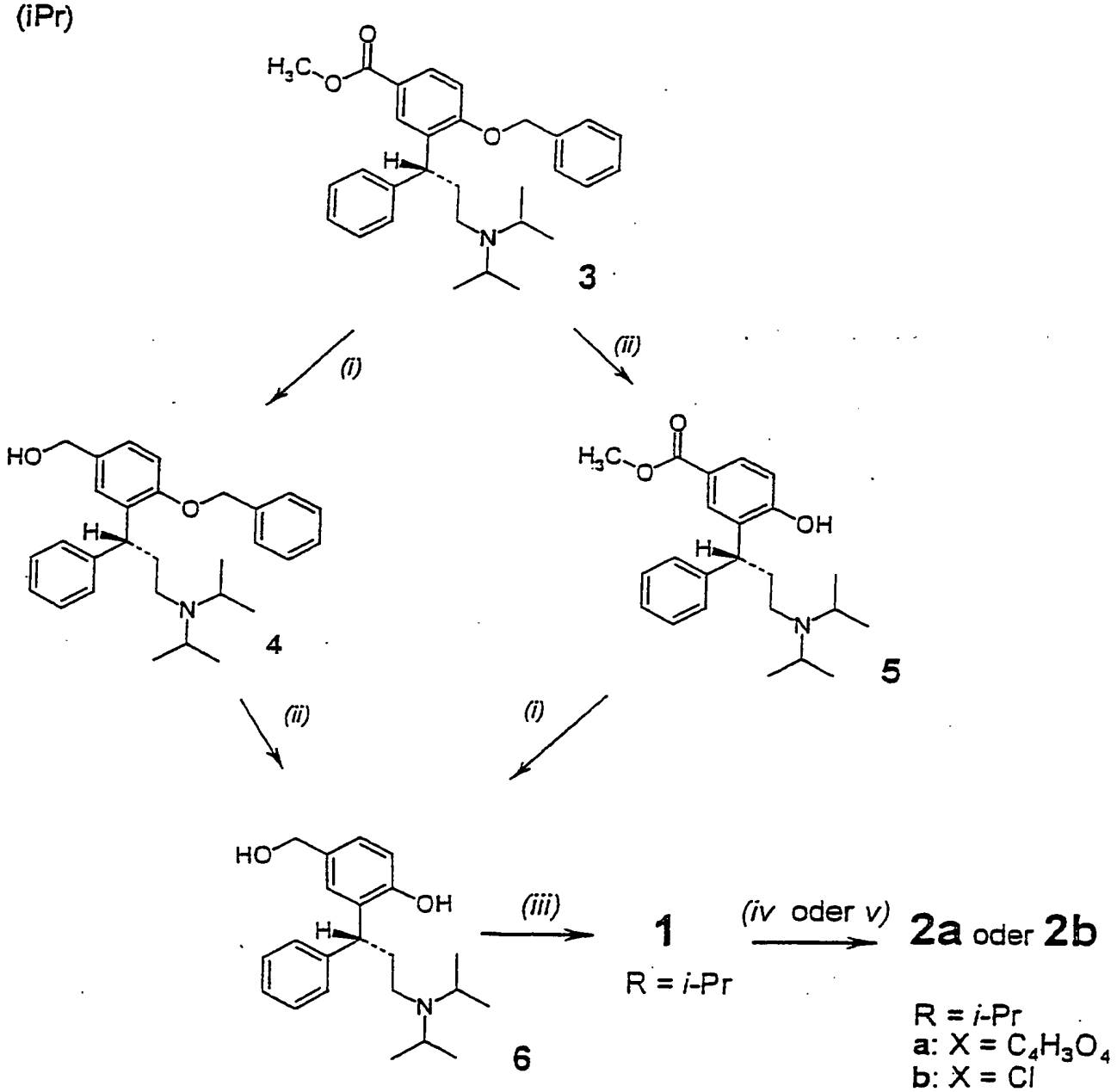
29. Verwendung einer Verbindung nach den Ansprüchen 23 bis 26 als Zwischenprodukt bei der Herstellung von Salzen phenolischer Monoester der allgemeinen Formel 2, in der R die gleiche Bedeutung hat, wie sie in Anspruch 3 angegeben ist.

30. Verwendung einer Verbindung nach den Ansprüchen 23 bis 26 als Zwischenprodukt bei der Herstellung von *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und *R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat.

FIGUR 1

Reaktionsschema 1

(i), (ii), (iii), (iv), (v) stehen für: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-COCl, Et_3N, (iv), Fumarsäure, (v), Salzsäure; R steht für Isopropyl (iPr)



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(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: **MEESE, Claus** [DE/DE]; Kreuzbergerstrasse 50, 40789 Monheim (DE).

(74) Anwalt: **ALBRECHT, Thomas**; Kraus & Weisert, Thomas-Wimmer-Ring 15, 80539 München (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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(54) **Title:** STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

(54) **Bezeichnung:** STABILE SALZE NEUARTIGER DERIVATE VON 3,3-DIPHENYLPROPYLAMINEN

(57) **Abstract:** The invention relates to highly pure, crystalline, stable compounds of 3,3-diphenylpropylamine derivatives, in the form of their salts, a method for their production and highly pure, stable, intermediate products. The method is particularly characterized by regio- and chemo-selectivity and high yields and provides salts of phenolic monoesters of 3,3-diphenylpropylamines, which are particularly suitable for application in technical pharmaceutic formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrogenfumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrochloride hydrate. The method further provides essential, stable, crystalline intermediate products for the production of the above salts. A preferred intermediate product is *R*-(-)-3-(3-diisopropylaminophenylpropyl)-4-hydroxybenzoic acid methyl ester.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft hochreine, kristalline, stabile Verbindungen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze, Verfahren zu deren Herstellung sowie hochreine, stabile Zwischenprodukte. Insbesondere zeichnet sich das Verfahren durch Regio- und Chemoselektivität sowie hohe Ausbeute aus. Es werden Salze phenolischer Monoester von 3,3-Diphenylpropylaminen zur Verfügung gestellt, die sich besonders gut zum Einsatz in pharmazeutisch-technischen Formulierungen eignen. Bevorzugte Verbindungen sind *R*-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat. Weiterhin werden stabile, kristalline verfahrenswesentliche Zwischenprodukte zum Erhalt der vorgenannten Salze zur Verfügung gestellt. Ein bevorzugtes Zwischenprodukt ist *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/11309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C215/54 C07C219/28

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)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 43942 A (HARALDSSON MARTIN ;PHARMACIA & UPJOHN AB (SE); RINGBERG ERIK (SE);) 8 October 1998 (1998-10-08) page 76, line 7,8 page 36, line 32,33 ---	19,20, 24,25
X	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) page 12, line 15,16,29,30 page 8, line 13-16 ---	18,20, 23,25
X	PALMER, L. ET AL.: "Determination of tolterodine and the 5-hydroxymetylmetabolite ..." J. PHARM. BIOMED. ANAL., vol. 16, 1997, pages 155-165, XP000995770 figure 1 -----	20

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2001	11/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTE TIONAL SEARCH REPORT

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ational Application No
PCT/EP 00/11309

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BR 9808069 A	08-03-2000
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		DE 69317898 T	15-10-1998
		DK 667852 T	11-01-1999
		EP 0667852 A	23-08-1995
		ES 2117155 T	01-08-1998
		FI 952179 A	05-05-1995
		HK 1006349 A	19-02-1999
		HU 72742 A	28-05-1996
		JP 8503208 T	09-04-1996
		NO 951775 A	05-05-1995
		US 5559269 A	24-09-1996
		US 5686464 A	11-11-1997

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 00/11309

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C07C215/54 C07C219/28

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C07C

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 98 43942 A (HARALDSSON MARTIN ;PHARMACIA & UPJOHN AB (SE); RINGBERG ERIK (SE);) 8. Oktober 1998 (1998-10-08) Seite 76, Zeile 7,8 Seite 36, Zeile 32,33 ---	19,20, 24,25
X	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26. Mai 1994 (1994-05-26) Seite 12, Zeile 15,16,29,30 Seite 8, Zeile 13-16 ---	18,20, 23,25
X	PALMER, L. ET AL.: "Determination of tolterodine and the 5-hydroxymetylmetabolite ..." J. PHARM. BIOMED. ANAL., Bd. 16, 1997, Seiten 155-165, XP000995770 Abbildung 1 -----	20

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
24. April 2001	11/05/2001

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffen... ...unge... ...ur selben Patentfamilie gehören

...tionales Aktenzeichen
PCT/EP 00/11309

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie			Datum der Veröffentlichung
WO 9843942	A	08-10-1998	AU	6755298	A	22-10-1998
			BR	9808069	A	08-03-2000
			CN	1251569	T	26-04-2000
			EP	1019358	A	19-07-2000
			NO	994438	A	26-11-1999
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			AU	672458	B	03-10-1996
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			DE	69317898	D	14-05-1998
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			NO	951775	A	05-05-1995
			US	5559269	A	24-09-1996
			US	5686464	A	11-11-1997

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(32) Priority Date: 22 January 1988 (22.01.88)

(33) Priority Country: SE

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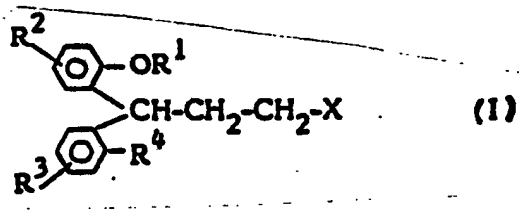
(74) Agents: KUMMELSTEN, Per, Arne et al.; Uppsala Patentbyrå, Box 9013, S-750 09 Uppsala (SE).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.

(54) Title: NEW AMINES, THEIR USE AND PREPARATION



(I)

(57) Abstract

Novel 3,3-diphenylpropylamines of formula (I) wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphan yl 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 and which together contain at least three carbon at ms, and which may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when th compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers, their use as drugs, especially as anticholinergic agents, their use for preparing an anticholinergic drug, pharmaceutical compositions containing the novel amines, and methods f r preparing the same.

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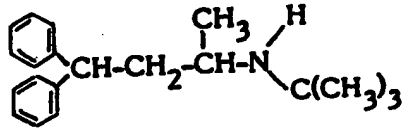
New amines, their use and preparation.

The present invention relates to novel 3,3-diphenylpropylamino d rivatives, to pharmaceutical compositi ns containing the same, and to the use of said derivatives for preparing drugs.

Swedish patent No. 215 499 discloses certain 3,3-diphenylpropylyamines having an advantageous effect on the heart and circulation. These pharmacologically active 3,3-diphenylpropylamines are secondary amines. Said Swedish patent also discloses certain chemical intermediates which are tertiary amines carrying aromatic substituents on the amine nitrogen. Neither the end products (secondary amines) nor the intermediates (tertiary amines) have any hydroxy or methoxy groups as substituents in the ortho positions of the phenyl rings, but only meta and para substituents are specifically disclosed.

It is known that terodiline, a commercially available drug having the chemical formula

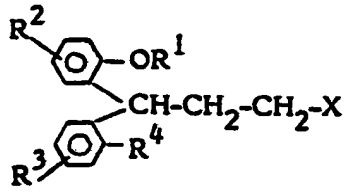


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect on the heart.

US-A-3.446.901, GB-A-1.169.944 and GB-A-1.169.945 disclose certain 3,3-diphenylpropylamine derivatives and pharmaceutical compositions having antidepressant activity, i.a. N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, which is considered to be the closest prior art as regards chemical structure (see also the comparative tests reported at the end of this specification). DK-A-111.894 discloses a special process for preparing certain diphenylalkylamines having an effect on the heart and circulation. The specifically described compounds are primary or secondary amines, and none of them has any hydroxy or alkoxy substituent in ortho position of the phenyl rings. C.A. Vol. 97 (1982) 120105n discloses certain N-arylalkylisoquinolines which may have a hydroxy substituent in the ortho position of a phenyl ring. These compounds hav sympatholytic activity and carry aromatic substituents on the nitrogen at m.

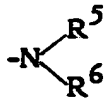
It is an bject f the present inventi n to provide a novel class f 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute t xicity.

In a first aspect the invention provides novel 3,3-diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



II

wherein R^5 and R^6 signify non-aromatic hydrocarbol 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^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom than the amine nitrogen.

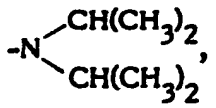
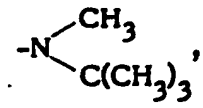
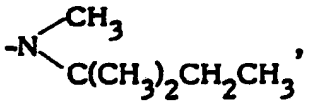
The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

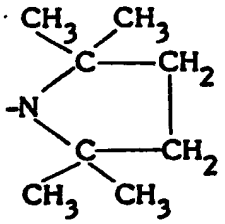
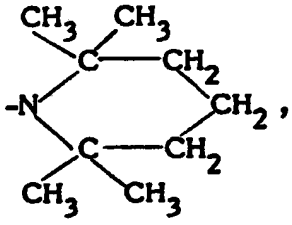
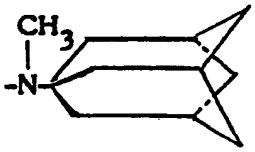
When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 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

f ll wing groups a) - f), each of which may carry one or more hydroxy groups.

a)  , b)  , c)  ,

d)  , e)  , f) 

The following are examples of presently preferred specific compounds of formula I:

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and its (+)-isomer,

N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

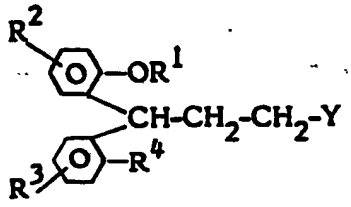
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,

N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine

In a second aspect the invention provides methods for preparing the compounds of formula I, especially the following methods:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III

 III

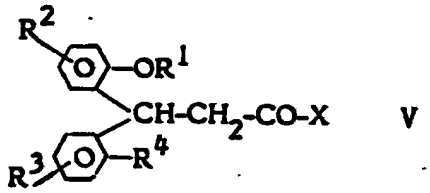
wherein R^1-R^4 are as defined above, and any hydroxy groups may be protected such as by methylation or benzylation, and wherein Y is a leaving gr up, preferably halogen or an alkyl or arylsulphonyloxy group,

with an amine of formula IV

H-X IV

wherein X is as defined above, or

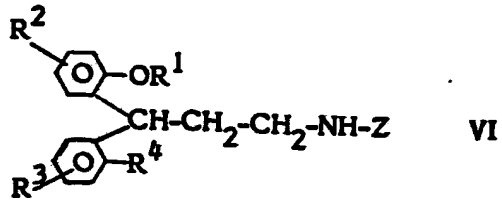
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride,

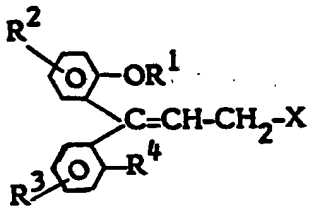
c) N-methylating a secondary 3,3-diphenylpropylamine VI



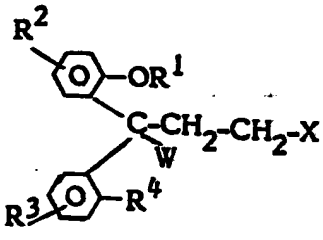
VI

wherein R^1-R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 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

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1-R^4 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, 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 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

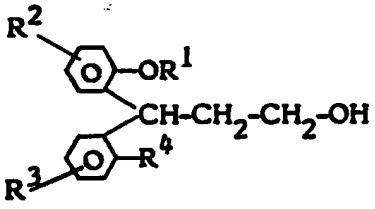
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

The above general methods can be carried out in a manner known per se and/or in accordance with the working examples described below, with due consideration of the desired amino groups and the substituents on the benzene rings.

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.

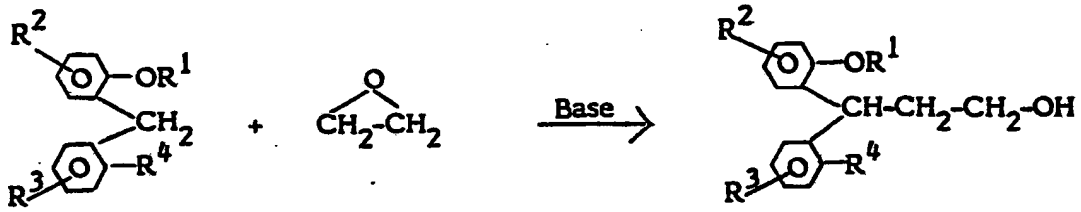
The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

Novel compounds of formula VIII



VIII

wherein R^1-R^4 are as defined above, and the corresponding protected compounds (e.g. comprising protected hydroxy groups), are useful as chemical intermediates for the preparation of e.g. the compounds of formula I, and they can be prepared by means of several different methods which are known per se, such as by addition of ethylene oxide (X) to a correspondingly substituted diphenylmethane (IX) in the presence of a suitable base such as sodium amide:



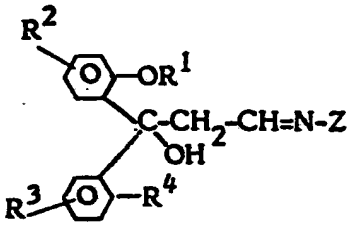
IX X VIII

The compounds VIII can also be prepared by reduction of the corresponding 3,3-diphenylpropionic acids, preferably using complex metal hydrides.

The 3,3-diphenylpropanols VIII can conveniently be converted into the corresponding reactively esterified derivatives III in a manner known per se by displacing the hydroxy groups with e.g. a halogen atom or an alkyl or arylsulphonyloxy group.

The 3,3-diphenylamides of formula V used as starting materials in method b), can e.g. be prepared by reacting the above mentioned 3,3-diphenylpropionic acids with an appropriate amine.

The secondary amines used as starting materials in method c) can conveniently be prepared by reacting a primary amine H_2N-Z (wherein Z is as defined above) with a corresponding reactively esterified 3,3-diphenylpropanol in analogy with method a) above, or by reduction of the corresponding secondary 3,3-diphenylpropionamides in analogy with method b) above. The secondary amines can also be prepared by reduction of unsaturated hydroxyamines XI



XI

wherein R^1-R^4 and Z are as defined above, either in one step by catalytic hydrogenation, or by reduction to the corresponding saturated hydroxyamine, preferably using a complex metal hydride such as lithium aluminium hydride, followed by removal of the hydroxy group by catalytic reduction. As an alternative, the hydroxy group may first be split off as water, followed by reduction of the formed unsaturated amine.

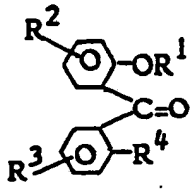
The unsaturated hydroxy amines XI can conveniently be prepared by the

additi n f a Schiff base of formula XII

$$CH_3\text{-}CH{=}N\text{-}Z \qquad XII$$

wherein Z is as defined above,

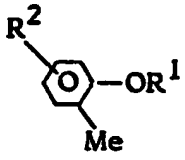
to a benzophenone of formula XIII



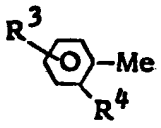
XIII

wherein R^1-R^4 are as defined above, in the presence of a base, preferably a lithium organic base such as lithium diisopropylamide.

Also the starting materials VIIa, VIIb for process d) can be prepared by methods known per se, such as by addition of an organometallic compound XIVa or XIVb

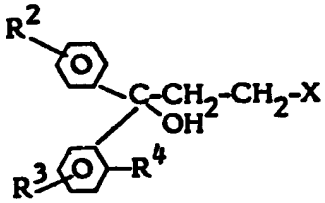


XIVa



XIVb

to a ketoamine XVa or XVb respectively to form a corresponding hydroxy amine XVI



XVI

and, if desired, splitting off water from compound XVI.

In formulae XIVa, XIVb, XVa, XVb, XVI, R^1-R^4 are as defined above, and Me signifies a metal such as magnesium or lithium.

In accordance with the 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, or the like, in acc rdance with accepted pharmaceutical procedur s. Such pharmaceuti-

cal compositi ns according to the invention comprise 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 mat rial, rganic r in rganic, 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 according to the invention can be used for treating cholin-mediated disorders such as urinary incontinence. As is well known, the dosage depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. The daily dosage may, for example, be from about 0.05 mg to about 4 mg per kilo of body weight, administered in one or more doses, e.g. containing from about 0.05 to about 200 mg each.

The inv ntion will be further illustrated by the following non-limiting examples.

General

^{1}H-NMR spectra were run in $CDCl_3$ using a JEOL PMX60 spectrom ter. In some cases, only a limited number of spectral peaks, useful for characterisation purposes, are reported.

Reported yields mostly refer to crude material of sufficient purity to be taken to the next stage.

Solvents are abbreviated as follows:

IPE = diisopropyl ether
PET = petroleum ether
Ether = diethyl ether

Amines are abbreviated as follows:

IPA = diisopropyl amine
TBA = tert.butyl amine

Melting points were taken on a Koefler bench.
Temperatures are in °C.
Water is used for the washing steps, unless otherwise stated.

Example 1

Preparation of 4-phenyl-3,4-dihydrocoumarins

a) 4-(2-Methoxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (I)

A mixture consisting of 2-methoxy-5-methylcinnamic acid (96.0 g, 0.5 mol), p-cresol (108 g, 1.0 mol), tetraline (200 ml), and conc. sulphuric acid (20 g) was heated slowly to refluxing temperature (145-150°). After 1 1/2 - 2 h, the mixture was cooled, taken up in ether, washed with water and sodium carbonate, dried and evaporated, giving 138 g (97%) crude oil. Two recrystallisations from acetone gave white crystals of the desired lactone, m.p. 126-127°.

$C_{18}H_{18}O_3$ (282.3) requires:	C	76.57	H	6.43	O	17.00
Found		76.9		6.44		17.0

b) 6-Hydroxy-4-phenyl-3,4-dihydrocoumarin (II) was prepared in a similar way in 97% yield from cinnamic acid and hydroquinone. M.p. 138° (IPE-Ether).

$C_{15}H_{12}O_3$ (240.3) requires:	C	74.99	H	5.04	O	19.98
Found		75.0		5.00		19.6

c) 4-(2-Methoxy-4-methylph nyl)-7-methyl-3,4-dihydrocoumarin was obtained in a similar way from 2-methoxy-4-methylcinnamic acid and m-cresol in 58%

yield. M.p. 147-148° (IPE-acetone).

$C_{18}H_{18}O_3$ (282.3) requires:	C	76.57	H	6.43	O 17.00
Found		76.4		6.31	17.2

Th above lactone (90 g, 0.32 m l) in methylene chloride (500 ml) was refluxed with BBr_3 (115 g, 0.46 mol) for 24 h, the solution was concentrated, the residue was taken up in ether, the solution was washed with sodium carbonate and water, dried and evaporated, giving 80 g (93%) of a syrup which crystallized on standing. Crystallization from IPE-PET gave white crystals of

d) 4-(2-hydroxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin (III), m.p. 137°.

$C_{17}H_{16}O_3$ (268.3) requires:	C	76.10	H	6.01	O 17.89
Found		76.2		6.30	17.0

e) 8-Hydroxy-4-phenyl-3,4-dihydrocoumarin (IV) was obtained in a similar way from cinnamic acid and catechol in 18% yield. M.p. 136° (IPE).

$C_{15}H_{12}O_3$ (240.2) requires:	C	74.99	H	5.04	O 19.98
Found		75.0		5.01	19.9

f) 4-(2-Methoxyphenyl)-3,4-dihydrocoumarin (V) was obtained in a similar way in 45% yield from methyl 2-methoxycinnamate and phenol. The crude reaction mixture was contaminated with methyl 3-(4-hydroxyphenyl)-3-(2-methoxyphenyl)-propionate. After removal of this by-product with ice-cold NaOH, the title compound was obtained as an oil of sufficient purity to be taken to the next step.

Example 2

Preparation of 3,3-diphenylpropionic acid esters

a) Methyl 3-(2-methoxy-4-methylphenyl)-3-phenylpropionate (VI)

7-Methyl-4-phenyl-3,4-dihydrocoumarin (78 g, 0.327 mol) in 150 ml methanol and 150 ml acetone containing methyl iodide (100 g, 0.7 mol) and K_2CO_3 (55 g, 0.4 mol) was refluxed for 24 h, filtered, and the solvent was evaporated. The residue was dissolved in ether, the solution was washed with water, dried and evaporated giving 86 g (92%) of a viscous oil.

NMR: δ 6.6-7.2 (m 8H), 4.9 (t 1H), 3.8 (s 3H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 3H).

b) Methyl 3,3-bis-(2-methoxyphenyl)-propionate (VII) was obtained in the same way in 96% yield from the lactone (V) of Example 1f), m.p. 84-87° (IPE).

$C_{18}H_{20}O_4$ (300.4) requires:	C	71.98	H	6.71	O 21.3
Found		71.4		6.67	21.6

c) Methyl 3-(2,3-dibenzyloxyphenyl)-3-phenylpropionate (VIII) was obtained in a similar way in quantitative yield from the lactone (IV) of Example 1e) and benzyl chloride in methanol. In addition to K_2CO_3 the reaction mixture also contained some NaI. M.p. 72 (IPE).

$C_{30}H_{28}O_4$ (452.5) requires:	C	79.63	H	6.24	O	14.14
Found		79.9		6.15		14.1

d) Methyl 3-(2-benzyloxyphenyl)-3-phenylpropionate (IX) was obtained in a similar way as a viscous oil in 81% yield from 4-phenyl-3,4-dihydrocoumarin and benzyl chloride.

NMR: δ 7.2 (m 14H), 4.9 (s 2H, t 1H), 3.5 (s 3H), 3.0 (t 2H).

e) Methyl 3-(2-methoxy-5-methylphenyl)-3-phenylpropionate (X) was obtained in a similar way from 6-methyl-4-phenyl-3,4-dihydrocoumarin in 96% yield.

NMR: δ 7.4 (m 8H), 5.0 (t 1H), 3.9 (s 3H), 3.7 (s 3H), 3.2 (d 2H), 2.4 (s 3H).

f) Methyl 3,3-bis-(2-methoxy-5-methylphenyl)propionate (XI) was obtained in a similar way in quantitative yield from the lactone (I) of Example 1a) and methyl iodide.

NMR: δ 6.6-7.1 (m 6H), 5.1 (t 1H), 3.7 (s 6H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 6H).

g) Methyl 3-(2,5-dibenzyloxyphenyl)-3-phenylpropionate (XII) was obtained in a similar way in 90% yield from the lactone (II) of Example 1b) and benzyl chloride.

NMR: δ 6.8-7.4 (m 18H), 5.0 (s 4H, t 1H), 3.7 (s 3H), 3.1 (d 2H).

h) Methyl 3,3-bis-(2-benzyloxy-4-methylphenyl)propionate (XIII) was obtained in a similar way in 95% yield from the lactone (III) of Example 1d) and benzyl chloride. By GLC the product is homogenous, and by MS it has the correct M.W.

i) Ethyl 3-(2,4-dimethoxyphenyl)-3-phenylpropionate (XIV)

A mixture of ethyl cinnamate (88 g, 0.5 mol), dimethyl resorcinol (276 g, 2.0 mol) and conc. sulphuric acid (50 g) was stirred on a boiling water-bath for 2 h, whereafter all the volatile material was distilled off in vacuum. The residual oil was dissolved in ether, the solution was washed with sodium carbonate, dried, and evaporated giving 101 g (64%) of the title ester in the form of a viscous oil.

NMR: δ 6.4-7.2 (m 8H), 4.9 (t 1H), 4.0 (q 2H), 3.7 (s 6H), 3.0 (d 2H), 1.1 (t 3H).

j) Methyl 3,3-bis-(2,4-dimethoxyphenyl)propionate (XV) was obtained in a similar way from methyl 2,4-dimethoxycinnamate and dimethyl resorcinol. The product thus obtained contained about 23% of dimethyl resorcinol. It was taken

to the next step without further purification.

k) Methyl-3-(5-chloro-2-methoxyph nyl)-3-phenylpr pionate

6-Chloro-4-phenyl-3,4-dihydrocoumarin (435 g, 1.68 mol. Preparation: T. Manimaran & V.T. Ramakrishnan, Ind. J. Chem. B 18 (1979) 328) is added to a hot solution of sodium hydroxide (140 g, 3.5 mol) in water (500 ml). The solution is chilled to 25°C and dimethyl sulphate (442 g, 3.5 mol) is added dropwise during 1 h with stirring and cooling at 25-35°C. The mixture is stirred for an additional 2 h whereupon a solution of 100 g of sodium hydroxide in 500 ml of water is added and the mixture is stirred until a clear solution is obtained. An excess of concentrated hydrochloric acid is added to precipitate the methoxy acid, which separates as an oil which slowly crystallizes. It is filtered off, washed with water and dried. Crystallization from 2-propanol gives colourless crystals of 3-(5-chloro-2-methoxyphenyl)-3-phenyl propionic acid, m.p. 144°C. Yield 455 g.

The above acid (291 g, 1.0 mol) in 1 litre methanol containing 50 g concentrated sulphuric acid was refluxed for 8 h. The solvent was distilled off, the residue was taken up in ether, washed with water and sodium carbonat solution, dried and evaporated giving 300 g (100%) crude oil. Recrystallisation from IPE gave white crystals of the title compound, m.p. 65-66°.

$C_{17}H_{17}ClO_3$ (304,8) requires:	C 67.0	H 5.62	Cl 11.63
Found	68.1	5.82	11.7

Example 3

Preparation of 3,3-diphenylpropanols

a) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropanol (XVI)

The ester (VI) of Example 2a) (84 g, 0.295 mol) in 150 ml dry ether was added dropwise to a suspension of $LiAlH_4$ (11.3 g, 0.295 mol) in 300 ml dry ether. The mixture was stirred overnight, then decomposed by the careful addition first of 11 g of water, then of 15% NaOH until a white granular precipitate was formed. The mixture was filtered, the filtrate was washed with water, dried, and evaporated giving 71 g (91%) of an oil which crystallized on standing. Recrystallization from IPE-PET gave white crystals, m.p. 83°.

$C_{17}H_{20}O_2$ (256.4) requires:	C 79.65	H 7.88	O 12.48
Found	79.4	7.89	12.7

b) 3,3-Bis-(2-methoxyphenyl)propanol (XVII) was obtained in a similar manner in quantitative yield as a viscous oil from the ester (VII) of Example 2b).

c) 3-(2,3-Dibenzyl xyphenyl)-3-phenylpropan l (XVIII) was obtained in a

similar way as a viscous oil in 96% yield from the ester (VIII) of Example 2c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropan-1-ol (XIX) was obtained in a similar way as an oil in 78% yield from the ester (IX) of Example 2d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropanol (XX) was obtained in a similar way as an oil in quantitative yield from the ester (X) of Example 2e).
NMR: δ 6.8-7.4 (m 7H), 4.7 (t 1H), 3.8 (s 3H), 3.7 (m 2H), 2.3 (s 3H), 2.0-2.3 (m 2H).

f) 3,3-Bis-(2-methoxy-5-methylphenyl)propanol (XXI) was obtained in a similar way in 98% yield from the ester (XI) of Example 2f). M.p. 89° (IPE).

$C_{19}H_{24}O_3$ (300.4) requires:	C	75.97	H	8.05	O 15.98
Found		75.9		8.02	16.1

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropanol (XXII) was obtained in a similar way in 88% yield from the ester (XII) of Example 2g). M.p. 78° (IPE).

$C_{29}H_{28}O_3$ (424.5) requires:	C	82.05	H	6.65	O 11.31
Found		82.0		6.62	11.2

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)propanol (XXIII) was obtained in a similar way as an oil in 93% yield from the ester (XIII) of Example 2h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropanol (XXIV) was obtained as a golden oil in 92% yield from the ester (XIV) of Example 2i).
NMR: δ 6.5-7.2 (m 8H), 4.5 (t 1H), 3.8 (s 6H), 3.6 (m 2H), 2.0-2.6 (m 3H).

j) 3,3-Bis-(2,4-dimethoxyphenyl)propanol (XXV) was obtained in a similar way from the impure ester (XV) of Example 2j). By NMR, the product contains about 20% of dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)propanol (XXVI)

A Grignard reagent was prepared in the usual manner from o-bromoanisole (93.5 g, 0.5 mol) and magnesium (12 g, 0.5 mol) in 100 ml dry ether. A solution of p-fluorobenzaldehyde (62 g, 0.5 mol) in 100 ml ether was added dropwise to this solution. After about 1 h, the mixture was decomposed with NH_4Cl and worked up, giving 100.6 g (87%) of 4-fluoro-2'-methoxy-diphenylmethanol. Recrystallization from IPE-PET gave white crystals, m.p. 88°.

$C_{14}H_{13}FO_2$ (232.3) requires:	C	72.40	H	5.64	
Found		72.9		5.75	

The obtained carbinol (46.2 g, 0.2 mol) in 600 ml ethanol was hydrogenated in the presence of 4 g of 5% Pd/C catalyst. After about 5-6 h, the

reaction was complete and the mixture was worked up giving 40 g (93%) of 4-fluoro-2'-methoxy-diphenylmethane as a clear oil.

NMR: 6.8-7.2 (m 8H), 4.0 (s 2H), 3.8 (s 3H).

The obtained methane derivative (71 g, 0.33 m l) in 100 ml ether was added to a solution of $NaNH_2$ prepared in situ from sodium (8.5 g, 0.37 mol) in about 300 ml of NH_3. After about 1 h, a solution of ethylene oxide (17.5 g, 0.395 mol) in 75 ml ether was added dropwise. The mixture was stirred for 2 h, and most of the ammonia was then removed with a stream of air. Solid NH_4Cl was then added, followed by the addition of water. The organic phase was separated, washed with water and 2N HCl, dried and evaporated, giving 81.5 g (95%) of the title compound. M.p. 61° (IPE-PET).

$C_{16}H_{17}FO_2$ (260.3) requires:	C	73.82	H	6.58	
Found		74.1		6.77	

l) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropanol

The ester from Example 2k) (91.5 g, 0.3 mol) in 500 ml dry ether was added dropwise under nitrogen to $LiAlH_4$ (11.4 g, 0.3 mol) in 200 ml dry ether. The mixture was stirred at room temperature overnight, then decomposed with 11 g water and 11 g 15% NaOH solution. Work up gave 72.5 g (87.5%) colourless oil. Recrystallization from IPE gave white crystals of the title compound, m.p. 80°.

$C_{16}H_{17}ClO_2$ (276.8) requires:	C	69.43	H	6.19	Cl	12.81
Found		70.1		6.44		12.9

Example 4

Preparation of 3,3-diphenylpropyl-p-toluene sulphonates

a) 3,3-Bis-(2-methoxyphenyl)propyl-p-toluene sulphonate (XXVII)

The propanol (XVII) of Example 3b) (35 g, 0.128 mol) in 100 ml chloroform containing 30 ml pyridine was cooled to about -10° and then treated with p-toluene sulphonyl chloride (29 g, 0.15 mol). After standing in the cooler (about +5°C) overnight, the mixture was poured into ice-water, the organic phase was washed with water and cold 2N HCl, dried, and the solvent was distilled off at < 50°C, giving a crude oil in quantitative yield. Recrystallization from IPE gave white crystals of low and indefinite m.p.

$C_{24}H_{26}O_5S$ (426.5) requires:	C	67.58	H	6.14	S	7.52
Found		66.8		6.22		7.76

b) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXI) was obtained in quantitative yield from the propanol (XVI) of Example 3a).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXVIII) was obtained in a similar way as a thick oil in 88% yield from the propanol (XVIII) of Example 3c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXIX) was obtained in i similar way in 98% yield from the propanol (XIX) of Example 3d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXX) was obtained in quantitative yield from the propanol (XX) of Example 3e). M.p. 64° (IPE-PET).

$C_{23}H_{24}O_4S$ (396.5) requires:	C	69.67	H	6.10	S	8.09
Found		69.8		6.20		7.85

f) 3,3-Bis-(2-methoxy-5-methylphenyl)-propyl-p-toluene sulphonate (XXXII) was obtained in quantitative yield from the propanol (XXI) of Example 3f). M.p. 117° (acetone-PET).

$C_{26}H_{30}O_5S$ (454.5) requires:	C	68.7	H	6.65	S	7.05
Found		68.8		6.66		7.11

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXIII) was obtained in a similar manner in quantitative yield from the propanol (XXII) of Example 3g).

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)-propyl-p-toluene sulphonate (XXXIV) was obtained in a similar way in 86% yield from the propanol (XXIII) of Example 3h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXV) was in the same way obtained in 96% yield from the propanol (XXIV) of Example 3i).

j) 3,3-Bis-(2,4-dimethoxyphenyl)-propyl-p-toluene sulphonate (XXXVI) was obtained in the same manner from the propanol (XXV) of Example 3j). The product was contaminated with dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)-propyl-p-toluene sulphonate (XXXVII) was obtained in a similar way in 88% yield from the propanol (XXVI) of Example 3k). M.p. 67° (IPE).

$C_{23}H_{23}FO_4S$ (414.5) requires:	C	66.65	H	5.59	S	7.74
Found		67.1		5.69		7.78

l) 3-(2-Methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XLVIII)

A mixture of anisole (1080 g, 10 mol), benzyl alcohol (216 g, 2 mol) and p-toluene sulphonic acid (40 g) was refluxed for 2 h in an apparatus equipped with a water separator. Excess of anisole was then distilled off, the oily residue was dissolved in ether, washed with water and sodium carbonate, dried and fractionated, giving 304 g (77%) of a pale yellow oil, b.p. 115-118°/0.4 Torr. By NMR, it is a 1:1 mixture of o-methoxy and p-methoxy diphenyl methane. This material was converted to a mixture of the corresponding propanols by reaction with ethylene oxide, as in the preparation of the propanol (XXVI) of Example 3k). This mixture of propanols was then converted as described above to a mixture of p-toluene sulphonates from which the title-compound could be isolated in 35% yield after two recrystallizations from IPE. M.p. 108°.

$C_{23}H_{24}O_4S$ (396.5) requires:	C	69.67	H	6.10	S	8.09
Found		69.3		6.00		8.17

m) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate

The alcohol from Example 3l) (66 g, 0.24 mol) in 300 ml chloroform containing 75 ml pyridine was treated portionswise in the cold with p-toluene-sulphonyl chloride (55 g, 0.29 mol). The mixture was kept at 5°C for 18 h, solvent was evaporated under vacuum at < 50°, the residue was taken up in ether, washed with water and 2 N HCl, dried and evaporated giving 100 g (97%) of a straw-yellow syrup. Recrystallization from IPE gave the title compound, m.p. 89-90°.

$C_{23}H_{23}ClO_4S$ (430.96) requires:	C	64.10	H	5.38	S	7.44	Cl	8.23
Found		64.4		5.45		7.04		8.17

Example 5

Preparation of tertiary 3,3-diphenylpropylamines

a) N,N-Diisopropyl-3,3-bis-(2-methoxyphenyl)-propylamine (XXXVIII), hydrogen oxalate

The tosylate (XXVII) of Example 4a) (42.6 g, 0.1 mol) in 100 ml acetonitrile and 100 g (1.0 mol) diisopropylamine was heated in a pressure bottle at 80° for 4-6 days. Volatile material was then evaporated, the residue was treated with excess of 2N NaOH and extracted with ether. The extract was washed with water and extracted with 2N HCl. This extract was washed with ether, basified,

extracted with ether, washed with water, dried, decoloured, filtered, and evaporated, giving 24.0 g (68%) of a crude oil. This oil was converted to the oxalic acid salt by treating an acetone solution of the base with one equivalent of oxalic acid in acetone. M.p. 160-161° (acetone).

$C_{25}H_{35}NO_6$ (445.6) requires:	C	67.39	H	7.92	N	3.14	O	21.55
Found		67.2		8.22		2.94		21.9

b) N,N-Diisopropyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (XXXIX)

The free base was obtained in the same way in 75% yield from the tosylate (XXVIII) of Example 4c).

NMR: 6.9-7.2 (m 18H), 5.0 (s 4H), 0.9 (d 12H).

c) N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (XL), hydrogenfumarate

The free base was obtained in 69% yield from the tosylate (XXX) of Example 4e). It was converted to the fumaric acid salt in the usual manner. M.p. 176° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires:	C	71.17	H	8.20	N	3.07	O	17.6
Found		71.3		8.27		3.04		17.9

d) N,N-Diisopropyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (XLI), hydrogenfumarate

The free base was obtained in 25% yield from the tosylate (XXXI) of Example 4b). The fumaric acid salt had m.p. 147-148° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires:	C	71.17	H	8.20	N	3.07	O	17.6
Found		71.3		8.14		3.00		17.6

e) N,N-Diisopropyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (XLII), hydrochloride

The free base was obtained in 78% yield from the tosylate (XXXII) of Example 4f). It was converted to the hydrochloride with ethereal HCl in the ususal manner. M.p. 163-164° (acetone-ether).

$C_{25}H_{38}NO_2Cl$ (420.1) requires:	C	71.49	H	9.12	N	3.33	O	7.61	Cl	8.44
Found		71.6		9.08		3.27		7.93		8.36

f) N,N-Diisopropyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (XLIII)

The free base was obtained in 70% yield from the tosylate (XXXIII) of Example 4g).

NMR: δ 6.6-7.2 (m 18H), 5.0 (s 4H), 4.5 (t 1H), 1.0 (d 12H).

g) N,N-Diisopropyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (XLIV)

The free base was btained in 62% yield fr m the tosylate (XXXIV) f Exampl 4h).

NMR: δ6.8-7.2 (m 16H), 4.8 (s 4H, t 1H), 0.9 (d 12H).

h) N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (XLV)

The free base was obtained in 56% yield from the tosylate (XXXV) of Example 4i).

NMR: 6.5-7.3 (m 8H), 4.4 (t 1H), 3.8 (s 6H), 1.0 (d 12H).

i) N,N-Diisopropyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (XLVI)

The free base was obtained in 34% yield from the tosylate (XXXVI) of Example 4j).

NMR: δ6.5-7.3 (m 6H), 4.6 (t 1H), 3.9 (s 12H), 1.0 (d 12H).

j) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine XLVII)

The free base was obtained in 71% yield from the tosylate (XXXVII) of Example 4k).

k) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine (XLIX), hydrogen fumarate

The free base was obtained in 86% yield from the tosylate (XLVIII) of Example 4l) and was converted to the fumaric acid salt in the usual way. M.p. 134-136° (acetone-IPE) or 163-164° (methanol).

$C_{26}H_{36}NO_5$ (441.6) requires:	C	70.72	H	7.99	N	3.28	O	18.12
Found		70.8		7.93		3.28		18.1

l) N-[3-(2-Methoxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethyl-piperidine (LXIV)

This compound was obtained in the same way in 54% yield from the tosylate (XLVIII) of Example 4l) and 2,2,6,6-tetramethylpiperidine. M.p. 100° (IPE).

$C_{25}H_{35}NO$ (365.6) requires:	C	82.14	H	9.65	N	3.83
Found		82.0		9.62		3.57

m) N,N-diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) was heated for 4 days at 80° with diisopropylamine (50 g, 0.5 mol) in 100 ml acetonitrile, giving 23 g (64%) f crude title compound. By GC, it is at least 93% pure.

n) N-[3-(2-Benzyl xyph nyl)-3-phenylpropyl]-2,2,5,5-tetram thyl-pyrrolidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2,2,5,5-tetramethylpyrrolidine. It was obtained as a sticky oil, which was converted to the hydroxy analogue without further purification (Example 9ab)).

o) N-[3-(2-Benzyloxyphenyl)-3-phenylpropyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 4-hydroxy-2,2,6,6-tetramethylpiperidine, and it was obtained as a sticky oil which was converted to the hydroxy compound without further purification (Example 9ac)).

p) N-(2-Hydroxy-1,1-dimethylethyl)-3-(2-benzyloxyphenyl)-3-phenyl-propylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2-amino-2-methylpropanol. The solid product was crystallized from diisopropyl ether and melted at 103°C. It was used as start material in Example 7p).

$C_{26}H_{31}NO_2$(389.5) requires:	C	80.17	H	8.02	N	3.60	O	8.22
Found		80.0		8.09		3.69		8.51

q) N-(1-Adamantyl)-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 1-aminoadamantane. It was used as start material in Example 7q). The hydrochloridesemihydrate was prepared in acetonitrile and melted at 225°C.

$C_{32}H_{37}NO.HCl.1/2\ H_2O$ (497.1) requires:	C	77.31	H	7.91	N	2.82	O	4.83 Cl 7.13
Found:		77.3		8.23		2.65		5.04 7.14

Example 6

Preparation of secondary 3,3-diphenylpropylamines

a) N-tert.Butyl-3,3-bis-(2-methoxyphenyl)propylamine (L), hydrogen oxalate

The tosylate (XXVII) of Example 4a) was heated with a large excess of tert.butylamine as described in Example 5, giving the free base in 78% yield, which was converted to the oxalic acid salt in the usual manner. M.p. 135-136° (acet ne-eth r).

$C_{23}H_{31}NO_6$ (417.5) requires:	C	66.17	H	7.48	N	3.36	O	22.99	
Found		65.6		7.31		3.36		23.4	

b) N-tert.Butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LI), hydrochloride

The free base was obtained as above in 78% yield from the tosylate (XXVIII) of Example 4c). The HCl salt had m.p. 184–185° (acetone-methanol-IPE).

$C_{33}H_{38}NO_2Cl$ (516.1) requires:	C	76.79	H	7.42	N	2.71	O	6.20	Cl 6.87
Found		76.3		7.30		2.72		6.42	6.81

c) N-tert.Butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LII), hydrogen oxalate

The free base was obtained in 84% yield from the tosylate (XXIX) of Example 4d). The oxalic acid salt had m.p. 198° (acetone-ether).

$C_{28}H_{33}NO_5$ (463.6) requires:	C	72.54	H	7.18	N	3.02
Found		71.8		7.13		2.95

d) N-tert.Butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LIII), hydrochloride

The free base was obtained in 90% yield from the tosylate (XXX) of Example 4e). When treated with ethereal HCl, it gave a somewhat hygroscopic salt which seems to be associated with 1/4 mol of water. M.p. 171° (ethanol-ether).

$C_{21}H_{29}NO.HCl.1/4\ H_2O$ (352.5) (requires):	C	71.55	H	8.74	N	3.97	O	5.67	Cl 10.06
Found		71.8		8.72		4.05		5.57	10.1

e) N-tert.Butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LIV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXI) of Example 4b). The HCl-salt had m.p. 138–149° (methanol-isopropanol). It was associated with 3/4 mol of water.

$C_{21}H_{30}NOCl.3/4\ H_2O$ (361.5) requires:	C	69.77	H	8.80	N	3.88	Cl	9.81
Found		69.8		8.76		3.93		9.75

f) N-tert.Butyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXII) of Example 4f). The HCl-salt had m.p. 242° (acetone).

$C_{23}H_{34}NOCl$ (392.0) requires:	C	70.47	H	8.74	N	3.57	Cl	9.05
Found		70.2		8.81		3.46		8.99

g) N-tert.Butyl-3-(2,5-dibenzyloxyph nyl)-3-phenylpropylamine (LVI), hydrochloride

The fre base was obtained in 85% yield from the tosylat (XXXIII) of Example 4g). Th HCl salt had m.p. 188° (ethanol- ther).

$C_{33}H_{38}NO_2Cl$ (516.1) requires:	C	76.79	H	7.42	N	2.71	O	6.20	Cl	6.87
Found		77.2		7.50		2.64		6.53		6.85

h) N-tert.Butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)-propylamine (LVII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXIV) of Example 4h). The HCL-salt had m.p. 210° (acetone-ether).

$C_{35}H_{42}NO_2Cl$ (544.2) requires:	C	77.25	H	7.78	N	2.57	O	5.89	Cl	6.52
Found		77.6		7.82		2.35		6.08		6.55

i) N-tert.Butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LVIII), hydrochloride

The free base was obtained in 84% yield from the tosylate (XXXV) of Example 4i). The HCl-salt had m.p. 196° (acetone-ethanol-ether).

$C_{21}H_{30}NO_2Cl$ (363.9) requires:	C	69.31	H	8.31	N	3.85	O	8.79	Cl	9.74
Found		69.3		8.44		3.80		8.89		9.81

j) N-tert.Butyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (LIX), hydrochloride

The free base was obtained in 60% yield from the tosylate (XXXVI) of Example 4j). The HCl-salt had m.p. 251° (methanol-acetone).

$C_{23}H_{34}NO_4Cl$ (424.0) requires:	C	65.15	H	8.08	N	3.30	O	15.09	Cl	8.36
Found		64.5		8.06		3.57		15.3		8.67

k) N-tert.Butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LX), hydrochloride

The free base was obtained in 89% yield from the tosylate (XXXVII) of Example 4k). The HCl-salt had m.p. 194° (ethanol-acetone).

$C_{20}H_{27}NOFCl$ (351.9) requires:	C	68.26	H	7.73	N	3.98			Cl	10.08
Found		68.9		7.97		4.01				9.69

l) N-tert.Butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXI), hydrochloride

The free base was obtained in 88% yield from the tosylate (XLVIII) of Example 4l). The HCl-salt had m.p. 205°.

$C_{20}H_{28}NOCl$ (333.9) requires:	C	71.94	H	8.45	N	4.20	O	4.79	
Found		71.9		8.44		4.67		4.79	

m) N-(1,1-Dimethylpropyl)-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXII), hydrochloride

The free base was obtained in 95% yield from the tosylate (XXX) of Example 4e) and tert. amylamine. The HCl-salt had m.p. 188-189° (ethanol-acetone).

$C_{22}H_{32}NOCl$ (362.0) requires:	C	73.00	H	8.91	N	3.87	O	4.42	Cl 9.80
Found		73.4		8.98		3.83		4.61	9.51

n) N-(1,1-Dimethylpropyl)-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXII) of Example 4f) and tert. amylamine. The HCl-salt had m.p. 210° (ethanol-acetone).

$C_{24}H_{36}NO_2Cl$ (406.0) requires:	C	71.00	H	8.94	N	3.45	O	7.88	Cl 8.73
Found		71.1		9.01		3.60		7.92	8.73

o) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) in 100 ml acetonitrile was treated with tert.butylamine (37 g, 0.5 mol) and the mixture was heated in a pressure bottle at 80° for 4 days. The usual work-up afforded 32 g (100%) crude title compound. The base in ether-acetone was treated with ethereal HCl giving the hydrochloride salt, m.p. 216-218°.

$C_{20}H_{26}ClNO.HCl$ (368.36) requires:	C	65.21	H	7.39	N	3.80	Cl	19.25	
Found		65.1		7.39		3.90		18.7	

Example 7

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

a) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXV), hydrochloride

A mixture of the secondary amine (LXI) of Example 6l) (29.7 g, 0.1 mol), formic acid (13.8 g, 0.3 mol), and 37% formaldehyde solution (12.5 g, 0.12 mol) was refluxed for 18-24 h. The mixture was then cooled, basified with NaOH, and extracted with ether. The extract was washed with water, dried and evaporated, giving 29.3 g (94%) of a crude oil. The HCl-salt was prepared from ethereal HCl in the usual way, m.p. 199°.

$C_{21}H_{30}NOCl$ (347.9) requires:	C	72.49	H	8.69	N	4.03	Cl	10.19	
Found		71.9		8.79		4.23		10.1	

b) N-Methyl-N-tert.butyl-3-(2-m thoxy-5-methylphenyl)-3-phenyl-propylamine (LXVI), hydrochloride

The free base was obtained in th sam way in 89% yield fr m th amine (LIII) f Example 6d). The HCl-salt had m.p. 161° (acetone).

$C_{22}H_{32}NOCl$ (362.0) requires:	C	73.00	H	8.91	N	3.87	O	4.42	Cl 9.08
Found		73.0		8.96		3.94		4.59	9.77

c) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxyphenyl)propylamine (LXVII), hydrochloride

The free base was obtained in 96% yield from the amine (L) of Example 6a). The HCl-salt had m.p. 187-190° (acetone-ether).

$C_{22}H_{33}NOCl$ (378.0) requires:	C	69.91	H	8.54	N	3.71	O	8.47	Cl 9.38
Found		69.9		8.56		3.53		8.93	8.92

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropyl-amine (LXVIII)

The free base was obtained in 96% yield from the amine (LIV) of Example 6e). M.p. 64° (IPE).

$C_{22}H_{31}NO$ (325.5) requires:	C	81.17	H	9.60	N	4.30	O	4.92	
Found		81.0		9.83		4.15		5.03	

e) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxy-5-methylphenyl)propyl-amine (LXIX)

The free base was obtained in 97% yield from the amine (LV) of Example 6f). M.p. 95° (IPE).

$C_{24}H_{35}NO_2$ (370.0) requires:	C	78.00	H	9.55	N	3.79	O	8.66	
Found		78.1		9.57		3.70		8.80	

f) N-Methyl-N-tert.butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LXX), hydrochloride

The free base was obtained in 82% yield from the amine (LX) of Example 6k). The HCl-salt had m.p. 218° (ethanol-acetone).

$C_{21}H_{29}NOClF$ (365.9) requires:	C	68.93	H	7.99	N	3.83	Cl	9.69	
Found		69.0		7.97		3.95		9.60	

g) N-(1,1-Dimethylpropyl)-N-methyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXXI), hydrochloride

The free base was obtained in 98% yield from the amine (LXII) of Example 6m). The HCl-salt had m.p. 176-177° (acetone).

$C_{23}H_{34}NOCl$ (376.0) requires:	C	73.47	H	9.11	N	3.73	Cl	9.43
Found		73.4		9.15		3.73		9.41

h) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LXXII), hydrochloride

The free base was obtained in 89% yield from the amine (LXIII) of Example 6n). The HCl-salt had m.p. 147° (acetone-ether).

$C_{25}H_{37}NO_2Cl$ (420.1) requires:	C	71.49	H	9.12	N	3.34	O	7.62	Cl 8.44
Found		70.8		9.20		3.63		7.74	8.42

i) N-Methyl-N-tert.butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropyl-amine (LXXIII)

This compound was obtained as an oil in quantitative yield from the amine (LVIII) of Example 6i).

NMR: 6.5-7.3 (m 8H), 4.3 (t 1H), 3.8 (s 6H), 2.3 (s 3H), 1.0 (s 9H).

j) N-Methyl-N-tert.butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropyl-amine (LXXIV)

This was obtained as an oil in 95% yield from the amine (LVI) of Example 6g).

k) N-Methyl-N-tert.butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propyl-amine (LXXV), hydrochloride

The free base was obtained in 92% yield from the amine (LVII) of Example 6k). The HCl-salt had m.p. 170-171° (acetone-ether).

$C_{36}H_{44}NO_2Cl$ (558.2) requires:	C	77.46	H	7.95	N	2.51	O	5.73	Cl 6.35
Found		77.6		7.86		2.42		5.89	6.31

l) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (LXXVI), hydrochloride

The free base was obtained in 96% yield from the amine (LIX) of Example 6j). The HCl-salt had m.p. 180-190° and seems to be associated with 1/4 mol of water.

$C_{24}H_{36}NO_4Cl$ 1/4 H_2O (447.0) requires:	C	64.48	H	8.34	N	3.13	O	16.11	Cl 7.93
Found		64.5		8.27		3.02		16.2	8.19

m) N-Methyl-N-tert.butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropyl-amine (LXXVII)

This was obtained as an oil in 98% yield from the amine (LI) f Example 6b).

NMR: δ6.9-7.3 (m 18H), 2.1 (s 3H), 1.0 (s 9H).

n) N-Methyl-N-tert.butyl-3-(2-benzyloxyphenyl)-3-phenylpropyl-amine (LXXVIII)

This was obtained as an oil in 97% yi ld from the amine (LII) of Example 6c).

NMR: 6.9-7.3 (m 14H), 5.0 (s 4H), 4.5 (t 1H), 2.2 (s 3H), 0.9 (s 9H).

o) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropyl-amine

The secondary amine from Example 6o) (25.3 g, 0.076 mol) was refluxed for 18 h with formic acid (9.2 g, 0.2 mol) and 35% formaldehyde solution (8.5 g, 0.1 mol). Work-up gave 25.6 g, (97.5%) crude base. This was dissolved in acetone and treated with an equimolar quantity of oxalic acid in acetone giving beige crystals of the title compound, hydrogen oxalate, m.p. 165°.

$C_{21}H_{28}ClNO.C_2H_2O_4$ (436.0) requires:	C	63.37	H	6.94	N	3.21	Cl	8.13
Found		62.7		6.83		3.10		7.97

p) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5p). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ad).

q) N-1-Adamantyl-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5q). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ae) without further purification.

Example 8

Preparation from olefinic precursors

a) N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenylpropylamine (LXXIX)

A solution of diisopropylamine (10.1 g, 0.1 mol) in dry ether (100 ml) was cooled to -10°. A solution of butyl lithium in hexane (65 ml, 0.1 mol) was added, and the mixture was stirred at -10° for 20 min. A solution of N-ethylidene-tert.butylamine (10 g, 0.1 mol) in dry ether (100 ml) was added and the solution was stirred at 0° for 20 min. After cooling to -30° a solution of 2,6-dimethoxybenzophenone (24.1 g, 0.1 mol) in dry ether (100 ml), containing 30 ml THF, was added. The mixture was then stirred at ambient temperature for 20 h and hydrolized with water. The organic phase was washed with water, dried and evap rated, giving 32 g (94%) of N-(3-(2,6-dimeth xyphenyl)-3-hydroxy-3-phenyl-propylidene)tert.butylamine as an oil.

This oil was dissolved in absolute ethanol (250 ml), the solution was cooled to -5°, and $NaBH_4$ (5.7 g, 0.15 mol) was added portionwise. The mixture was stirred at 0 for 1/2 h, then at ambient temperature for 3 h. Most of the solvent was distilled off in vacuum, the residue was treated with water, extracted with ether, washed with water, and extracted with 2N HCl. The extract was washed with ether, basified with NaOH, extracted with ether, dried and evaporated, giving 30 g of the title amine.

The HCl-salt had m.p. 203-204° (acetone-ether) and seems to be associated with 1/4 mol of water.

$C_{21}H_{29}NO_3.HCl.1/4\ H_2O$ (384.5) requires: C 65.60 H 8.01 N 3.64 O 13.52
Found 65.9 8.11 3.64 13.7

b) N-tert.Butyl-3-(2,6-dimethoxyphenyl)-3-phenyl-2-propene-1-amine (LXXX)

The above amine from step a) (21 g, 0.061 mol) was added to 6.3N H_2SO_4 (20 ml, 0.126 mol). The mixture was stirred on a boiling water bath for 2 h, cooled, basified, and extracted with ether. The extract was washed, dried and evaporated, giving 17.8 g, (90%) of the title olefin as a clear oil. The HCl-salt had m.p. 220-22°, and was associated with 1/4 mol of water.

$C_{21}H_{27}NO_2.HCl.\ 1/4\ H_2O$ requires: C 68.82 H 7.86 N 3.82 O 9.82 Cl 9.68
Found 68.8 7.89 3.92 9.81 9.44

c) N-Methyl-N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropyl-amine (LXXXI), hydrogen fumarate

The olefinic amine from step b) (16.3 g, 0.05 mol) in methanol (250 ml) containing 0.5 g of a 10% Pd/C catalyst, was hydrogenated at ambient temperature and pressure. The mixture was then filtered through Celaton, the filtrate was taken to dryness, giving 16.3 g (100%) of N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine. The HCl-salt had m.p. 244° (ethanol).

$C_{21}H_{29}NO_2.HCl$ (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.3 8.29 3.83 9.27 9.75

The above secondary amine, as the free base, was methylated with formaldehydeformic acid as described in Example 7, giving the tertiary amine in 96% yield. The fumaric acid salt had m.p. 185-190° (acetone).

$C_{26}H_{35}NO_6$ (457.6) requires: C 68.25 H 7.71 N 3.06 O 20.95
Found 67.8 7.59 3.05 21.6

Example 9

Rem val of O-pr tective groups

a) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamin (LXXXII), hydrochloride

The amine (XLIX) of Example 5k) (20.8 g, 0.064 mol) in methylene chloride (150 ml) was cooled below 0°. A 1N solution of BBr_3 in CH_2Cl_2 (64 ml, 0.064 mol) was then added dropwise, the solution was then kept in the cooler (5°) for 2-5 days, and volatile material was distilled off at <50°. The residual syrup was basified, extracted with ether, the extract was washed with water, dried and evaporated, giving a viscous syrup. The HCl-salt had m.p. 222° (methanol-ether), yield 31%.

$C_{21}H_{29}NO.HCl$ (347.9) requires:	C	72.49	H	8.69	N	4.03	O	4.60	Cl 10.19
Found		72.0		8.72		3.74		5.06	10.3

The following compounds were obtained in the same way.

b) N-[3-(2-Hydroxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethyl-piperidine (LXXXIII), hydrogen fumarate

From the amine (LXIV) of Example 5l). Crude yield 78%. M.p. fumaric acid salt = indefinite.

$C_{28}H_{37}O_5$ (467.6) requires:	C	71.9	H	7.91	N	3.00	O 17.1
Found		71.8		8.41		3.01	16.6

c) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXIV), hydrochloride

From the amine (XL) of Example 5c). Crude yield 85%. HCl-salt, m.p. 209-210° (acetone-ether).

$C_{22}H_{31}NO.HCl.\ 1/4\ H_2O$ (366.5) requires:	C	72.09	H	8.95	N	3.82	O	5.46	Cl 9.67
Found		72.3		8.95		3.71		5.68	9.61

d) N-Methyl-N-tert.butyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl-propylamine (LXXXV), hydrochloride

From the amine (LXVI) of Example 7b). Crude yield 100%. HCl-salt, m.p. >260° (ethanol).

$C_{21}H_{29}NO.HCl$ (347.4) requires:	C	72.49	H	8.69	N	4.03	Cl 10.19
Found		72.7		8.58		3.81	10.95

e) N,N-Diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine (LXXXVI), hydrochloride

From the amine (XXXVIII) of Example 5a). Crude yield 57%. HCl-salt, m.p. 257° (ethanol-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
F und 69.3 8.37 3.95 9.23 9.40

f) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine (LXXXVII), hydrochloride

From the amine (LXVII) of Example 7c). Crude yield 100%, m.p. 190°. HCl-salt, m.p. 252° (ethanol).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C 68.65 H 8.06 N 4.00 Cl 10.13
Found 68.4 8.06 4.17 9.59

g) N,N-Diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (LXXXVIII), hydrochloride

From the amine (XLI) of Example 5d). Crude yield 90%. HCl-salt, m.p. 217° (ethanol).

$C_{22}H_{31}NO$.HCl. 1/4 H_2O (366.5) requires: C 72.09 H 8.96 N 3.82 O 5.46 Cl 9.67
Found 72.3 8.91 3.93 5.27 9.46

h) N,N-Diisopropyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (LXXXIX), hydrochloride

From the amine (XLII) of Example 5e). Crude yield 93%, m.p. 166°. HCl-salt, m.p. 220° (ethanol).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C 70.47 H 8.74 N 3.57 Cl 9.05
Found 70.6 8.78 3.71 8.93

i) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XC), hydrochloride

From the amine (LXIX) of Example 7e). Crude yield 79%, m.p. 199-201° (IPE). HCl-salt, m.p. 220° (acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C 69.91 H 8.54 N 3.71 O 8.47 Cl 9.38
Found 69.9 8.70 3.75 8.81 9.15

j) N-Methyl-N-tert.butyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (XCI), hydrochloride

From the amine (LXVIII) of Example 7d). Crude yield 100%. HCl-salt, m.p. 240° (ethanol).

$C_{21}H_{29}NO$.HCl (347.9) requires: C 72.49 H 8.69 N 4.03 O 4.60 Cl 10.19
Found 72.5 8.75 4.06 4.90 10.1

k) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-hydr xyphenyl)propylamine (XCII), hydrochl ride

From the amine (XLVII) of Example 5j). Crude yield 72%. HCl-salt, m.p.

183° (acetone-ethanol).

$C_{21}H_{27}FNO.HCl$ (364.9) requires:	C	69.12	H	7.73	N	3.83			
Found		69.1		8.09		3.82			

l) N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCIII), hydrochloride

From the amine (XLV) of Example 5h). Crude yield 31%. HCl-salt, m.p. 205-210° (ethanol-acetone-ether).

$C_{21}H_{29}NO_2.HCl$ (363.9) requires:	C	69.31	H	8.31	N	3.85	O	8.79	Cl 9.74
Found		69.5		8.33		3.72		8.91	9.87

m) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-hydroxy-5-methylphenyl)-propylamine (XCIV), hydrochloride

From the amine (LXXII) of Example 7h). Crude yield 100%, m.p. 190-195°. HCl-salt, m.p. 235-240° (ethanol-acetone-ether).

$C_{23}H_{33}NO_2.HCl$ (392.0) requires:	C	70.47	H	8.74	N	3.57	O	8.16	Cl 9.05
Found		70.0		8.96		3.54		8.11	9.19

n) N-Methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCV), hydrobromide

From the amine (LXXIII) of Example 7i). Crude yield 78%, m.p. 260°. HBr-salt, m.p. >260° (ethanol).

$C_{20}H_{25}NO_2.HBr$ (394.4) requires:	C	60.9	H	7.16	N	3.55	O	8.11	Br 20.27
Found		60.8		7.18		3.29		8.38	20.2

o) N,N-Diisopropyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVI), hydrochloride

From the amine (XLVI) of Example 5i). The HCl-salt, consisting of an amorphous brown powder, did not give a satisfactory elemental analysis because of incomplete combustion.

p) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVII), hydrochloride

From the amine (LXXVI) of Example 7l). Crude yield 87%, m.p. 260°. The HCl-salt did not give a satisfactory elemental analysis because of incomplete combustion.

q) N,N-Diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCVIII), hydrochloride

The amine (XLIII) of Example 5f) in the form of the free base (32 g, 0.063 mol) in methanol (500 ml) containing 5 g of a 5% Pd/C catalyst was hydrogenated

at ambient temperature and pressure. After 2 h the reaction was complete. The mixture was filtered, the filtrate was taken to dryness, the residue was dissolved in acetone and treated with ethereal HCl, giving 19.8 g (87%) of a crude salt, m.p. 260°. Recrystallization from methanol gave white crystals, m.p. 260°.

$C_{21}H_{29}NO_2$.HCl. 1/4 H_2O (368.6) requires: C 68.44 H 8.36 N 3.80 O 9.77 Cl 9.62
Found 68.4 8.40 3.60 10.3 9.42

The following compounds were prepared in the same way.

r) N-Methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCIX), hydrochloride

From the amine (LXXIV) of Example 7j). Crude yield 90%. HCl-salt, m.p. >270° (methanol-water).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C 68.65 H 8.06 N 4.00 O 9.14 Cl 10.13
Found 68.9 8.02 3.93 9.60 10.5

s) N,N-Diisopropyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (C), hydrochloride

From the amine (XLIV) of Example 5g). Crude yield 100%. HCl-salt, m.p. 253° (methanol-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C 70.47 H 8.74 N 3.57 O 8.16 Cl 9.05
Found 70.5 8.74 3.55 8.47 8.03

t) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (CI), hydrochloride

From the amine (LXXV) of Example 7k). Crude yield 97%, a yellow powder. HCl-salt, m.p. 260° (methanol-acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C 69.91 H 8.54 N 3.71 O 8.47 Cl 9.38
Found 69.9 8.68 3.67 8.85 9.24

u) N,N-Diisopropyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CII), hydrochloride

From the amine (XXXIX) of Example 5b). Crude yield 100%. HCl-salt, m.p. 174-176° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C 69.31 H 8.31 N 3.85 O 8.79 Cl 9.74
Found 69.5 8.33 3.66 9.37 9.63

w) N-Methyl-N-tert.butyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CIII), hydrochloride

From the amine (LXXVII) of Example 7m). Crude yield 100%, a white powder. HCl-salt, m.p. 209-210°, slow heating, (methanol-acetone).

$C_{20}H_{27}NO_2$.HCl. 1/4 H_2O (358.9) r quires: C 66.92 H 8.14 N 3.90 O 11.14 Cl 9.88
Found 66.9 8.12 3.76 11.8 9.74

x) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (CIV), hydrochlorid

From the amine (LXXVIII) of Example 7n). Crude yield 100%. HCl-salt, m.p. 255° (acetone-ether).

$C_{20}H_{27}NO$.HCl (333.9) requires: C 71.94 H 8.45 N 4.20 Cl 10.62
Found 71.9 8.43 4.01 10.5

y) N-Methyl-N-tert.butyl-3-(2,6-dihydroxyphenyl)-3-phenylpropylamine (CV), hydrochloride

From the amine (LXXXI) of Example 8c) with BBr_3, in low yield. HCl-salt, m.p. 170° (ethanol-ether).

$C_{20}H_{27}NO_2$.HCl. 1/2 H_2O (358.9) requires: C 66.93 H 8.14 N 3.40 O 11.14 Cl 9.87
Found 67.4 8.28 3.63 10.9 9.99

z) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The base from Example 5m) (11.7 g, 0.032 mol) was treated with pyridine (7.6 g, 0.096 mol) and conc. HCl (13 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205-215° for 1 1/2 h. The melt was cooled somewhat, water was added, the mixture was digested in a boiling water bath and cooled. 2 N HCl was added, the salt was filtered off, washed with 2 N HCl and dried, giving 11.0 g (90%) white salt m.p. 200°. Recrystallization from acetone gave the hydrochloride of the title compound, m.p. 202-203°.

$C_{21}H_{28}ClNO$.HCl (382.4) requires: C 65.96 H 7.64 N 3.66 Cl 18.54
Found 66.0 7.88 3.63 18.3

aa) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The free base from Example 7o) (10.5 g, 0.03 mol) was treated with pyridine (7.0 g, 0.09 mol) and conc. HCl (12 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205-215° for 1 1/2 h. The melt was cooled somewhat, excess of 2 N NaOH was added, the mixture was extracted with ether, the extract was washed with water, dried and evaporated giving 7.5 g (88%) crude syrup. This was dissolved in ether and treated with ethereal HCl giving 8 g (83%) of hydrochloride salt. Recrystallizati n from acetone-2 N HCl gave the hydrochloride of the title compound, m.p. 260°.

$C_{20}H_{26}ClNO.HCl$ (368.4) requires: C 65.21 H 7.39 N 3.80 Cl 19.25
Found 65.0 7.30 3.73 18.9

ab) N-[3-(2-Hydr xyphenyl)-3-phenylpropyl]-2,2,5,5-tetramethyl-pyrr lidine

The crude amine from Example 5n) was hydrogenolysed as described in Example 9q). The free amine was obtained as an oil which was converted to the hydrochloride and crystallized from 2-propanol. M.p. 250°C.

$C_{23}H_{31}NO.HCl$ (374.0) requires: C 73.86 H 8.63 N 3.75 O 4.28 Cl 9.48
Found 73.8 8.71 3.59 4.80 9.45

ac) N-[3-(2-Hydroxyphenyl)-3-phenylpropyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine

The benzyloxy compound from Example 5o) was hydrogenolysed as described in Example 9q). The free base was converted to the hydrochloride semihydrate which was crystallized from acetone. The compound melts with decomposition at about 150°C.

$C_{24}H_{33}NO_2.HCl.\ 1/2\ H_2O$ (413.0) requires: C 69.79 H 8.54 N 3.39 O 9.68 Cl 8.58
Found: 70.0 8.67 3.47 9.98 8.13

ad) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7p) was hydrogenolysed as described in Example 9q). The amine, obtained as a glassy mass, was converted to the hydrochloride which was obtained as an amorphous solid on precipitation from ethanol with ether.

$C_{20}H_{27}NO_2.HCl$ (349.9) requires: C 68.65 H 8.06 N 4.00 O 9.15 Cl 10.13
Found: 68.25 8.18 3.98 9.12 10.0

ae) N-1-Adamantyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7q) was hydrogenolysed as described in Example 9q). The free hydroxyamine was obtained as a glassy mass. It was dissolved in anhydrous ether and treated with an excess of hydrogen chloride in ether. The hydrochloride precipitated as a powder which decomposed at about 220°C.

$C_{26}H_{33}NO.HCl$ (412.0) requires: C 75.79 H 8.32 N 3.40 O 3.88 Cl 8.61
Found: 75.3 8.01 3.22 3.45 8.96

Example 10

Reduction of amides

a) N,N-Diis propyl-3-(2-methoxy-5-methylph nyl)-3-phenylpropylamine

3-(2-Meth xy-5-methylphenyl)-3-phenylpropionic acid (12.8 g, 0.05 mol) (J.D. Simpson & H. Stehphen, J. Chem. Soc. 1956 1382) and thionyl chloride (50 ml) are heated on a water bath for 3 h. The excess of thionyl chloride is distilled off under reduced pressure. The remaining crude 3-(2-methoxy-5-methylphenyl)-3-phenylpropionyl chloride is dissolved in 50 ml of dichloromethane and added dropwise to a stirred solution of diisopropylamine (20.2 g, 0.20 mol) in 200 ml of dichloromethane at about 0°C. The solution is left for 2 h, the solvent is distilled off and the remaining material is treated with water. The solid product consisting of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropionamide is filtered off, dried and added in small portions to a stirred suspension of lithium aluminium hydride (6.0 g, 0.16 mol) in dry ether (700 ml). The mixture is refluxed for 2 days. Excess of hydride is destroyed by the careful addition of water, the ether layer is separated and dried with anhydrous sodium sulfate. After filtration the solution is added to a solution of excess fumaric acid in ether. The precipitated salt is collected and crystallized from 2-propanol. The hydrogen fumarate melts at 176°C.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine was similarly prepared. The hydrochloride melts at 161°C.

Example 11

a) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

A solution of chlorine (7,1 g, 0,10 mol) in acetic acid (500 ml) is added dropwise to a stirred solution of N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (29.7 g, 0.10 mol) in acetic acid (200 ml) with stirring. After 2 h the solvent is distilled off under reduced pressure and the crude hydrochloride left is recrystallized from 2-propanol. Melting point 260°C.

b) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared. The hydrochloride melts at 202-3°C.

Example 12

Separation of (+)- and (-)-enantiomers

(±)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (31.1 g, 0.10 mol) is dissolved in 300 ml of ethanol. A solution of L(+)-tartaric acid (15.0 g, 0.10 mol) in 400 ml of ethanol is added. The mixture is heated a few minutes in a boiling water bath and seeded with crystals obtained by cooling and

scratching a small sample of the main s lution. Th mixture is chilled at about 4°C over-night whereupon the crystalline precipitate is filtered ff, washed with cold ethanol and recrystallized repeatedly from ethanol. The pure (–)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine hydrogen L-(+)-tartrate thus obtained has $[\alpha]_D^{20}$ –10.6 (c = 5% in methanol). The free amine is obtained by alkalisation of an aqueous solution, extraction into ether, drying and evaporation of the solvent. Sticky oil, $[\alpha]_D^{20}$ –5.4° (c = 5% in methanol).

(+)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared using D-(-)-tartaric acid. The hydrogen-D-(-)tartrate has $[\alpha]_D^{20}$ +10.0°. The free amine has $[\alpha]_D^{20}$ +5.6°, both measured as 5% solutions in methanol.

Example 13 (continuation of Example 1)

Preparation of 4-phenyl-3,4-dihydrocoumarins

g) 4-(2-Methoxyphenyl)6-methyl-3,4-dihydrocoumarin (CVI)

A mixture of 2-methoxycinnamic acid (178 g, 1.0 mol), p-cresol (108 g, 1.0 mol), and p-toluenesulphonic acid monohydrate (47.5 g, 0.25 mol) was stirred on a boiling water-bath for about 2 h during which time the system was evacuated with a waterpump to remove formed water. The solid was then broken up and washed copiously with water. The granular material was then stirred with a large volume of saturated $NaHCO_3$ solution containing some 10% acetone. The product was filtered off, washed, dried and recrystallised from acetone affording 167 g (62,5%) white crystals of the desired lactone, m.p. 140°.

$C_{17}H_{16}O_3$ (268.3) requires:	C 76.10,	H 6.01,	O 17.89
Found:	76.0	5.97	17.9

h) 6-Chloro-4-(2-methoxyphenyl)-3,4-dihydrocoumarin (CVII) was prepared in a similar way in 49% yield from 2-methoxycinnamic acid and p-chlorophenol, the reaction temperature being 130° in this case. M.p. 172-173° (acetone).

$C_{16}H_{13}O_3$ (288.7) requires:	C 66.56	H 4.54	O 16.62
Found:	66.8	4.45	16.5

Example 14 (continuation of Example 2)

Preparation of 3,3-diphenylpropionic acid esters

l) Methyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propionate (CVIII) was obtained as an oil in 75% yield from the lactone CVI of Example 13g in the manner described for the ester VI of Example 2a).

m) Methyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propionate (CIX) was obtained as an oil in the same way in 97% yield from the lactone CVII of Example 13.

Example 15 (continuation of Example 3)

Preparation of 3,3-diphenylpropanols

m) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propanol (CX) was obtained in 84% yield from the ester CIX of Example 14m in the manner described for the propanol XVI of Example 3a), except that the reduction was carried out in toluene with a 10% molar excess of a 3.4 M toluenic solution of sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) instead of $LiAlH_4$. M.p. 70-72° (IPE).

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propanol (CXI) was obtained in the same way in quantitive yield from the ester CVIII of Example 14l). The product consisted of a golden oil of 89% purity according to GC.

Example 16 (continuation of Example 4)

Preparation of 3,3-diphenylpropyl-p-toluenesulphonates

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propyl-p-toluenesulphonate (CXII) was prepared in the same way as the tosylate XXVII of Example 4a) in quantitative yield from the propanol CXI of Example 15n) using CH_2Cl_2 as solvent instead of chloroform. M.p. 101° (ether/IPE).

$C_{25}H_{28}O_5S$ (440.57) requires:	C 68.16	H 6.41	S 7.28	
Found:	68.3	6.51	7.20	

o) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propyl-p-toluenesulphonate (CXIII) was obtained in the same way in quantitative yield from the propanol CX of Example 15m. M.p. 97-98° (acetone/IPE).

$C_{24}H_{25}ClO_5S$ (460.92) requires:	C 62.54	H 5.47	S 6.94	Cl 7.69
Found:	63.0	5.65	6.95	7.70

Example 17 (continuation of Example 5)

Preparation of tertiary 3,3-diphenylpropylamines

r) N,N-Diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)-propylamine (CXIV) was obtained as an oil in 94% yield from the tosylate CXIII of Example 16o) in the manner described for the amine XXXVIII of Example 5a). Purity by GC = 99.9%.

s) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)-propylamine (CXV) was obtained in the same way in 49% crude yield from the tosylate CXV of Example 16n). After chromatographic purification on an Si-gel 60 column (eluation with light petroleum), the product (oil)

had a purity of 100% according to GC.

t) N-[(2-Benzyloxy-5-methyl)-3-phenyl]-2,2,5,5-tetramethylpyrrolidine (CXVI) was prepared from 3-(2-benzyloxy-5-methyl)-3-phenylpropyl tosylate and 2,2,5,5-tetramethylpyrrolidine following the directions given in Example 5a). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 20aj).

Example 18 (continuation of Example 6)

Preparation of secondary 3,3-diphenylpropylamines

p) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXVII) was prepared in quantitative yield from the tosylate CXIII of Example 16o) in the manner described for the amine L of Example 6a). The HCl-salt had m.p. >260°.

$C_{21}H_{28}ClNO_2$.HCl (398.38) requires: C 63.3 H 7.34 N 3.52 Cl 17.80

Found: 63.2 7.46 3.49 17.4

q) N-tert.Butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXVIII) was obtained in a similar way in 89% crude yield from the tosylate CXII of Example 16n). The HCl-salt had m.p. 225°.

$C_{22}H_{31}O_2N$.HCl (377.97)

Requires:	C 69.91	H 8.54	N 3.71	Cl 9.38	O 8.47
Found:	69.8	8.73	3.60	9.45	8.79

Example 19 (continuation of Example 7)

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

r) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIX) was prepared in 89% yield from the amine CXVII of Example 18p) in the manner described for the amine LXI of Example 7a). The HCl-salt was prepared by treating an acetonic solution of the free base with conctrated hydrochloric acid. M.p. 130°.

$C_{22}H_{30}ClO_2N$.HCl.H_2O (430.42)

Requires:	C 61.39	H 7.74	N 3.25	Cl 16.47
Found:	62.0	7.93	3.26	16.5

s) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXX) was prepared in a similar way in 98% yield from the amine CXVIII of Example 18q). The free base (oil) had a purity of 96% by GC.

Example 20 (continuation of Example 9)

Removal of O-protective groups

af) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)-propylamine (CXXI)

The amine CXV from Example 17s) (26.5 g, 0.072 mol) in methanol was treated with a slight excess of concentrated hydrochloric acid. The mixture was taken to dryness in vacuum, pyridinium chloride (25.4 g, 0.22 mol) was added and the mixture was then heated at 200-205° for 1 ½ h. The mixture was cooled to about 80°, acetone (20 g) was added followed by addition of little water. The salt was filtered off, washed with diluted HCl and dried. Recrystallisation from absolute ethanol-/ether gave 17.5 g (64.3%) of a white salt, m.p. >250°. Purity by GC = 100%.

$C_{22}H_{31}NO_2$.HCl (377.97)

Requires:	C 69.91	H 8.54	N 3.71	O 8.47	Cl 9.38
Found:	69.8	8.65	3.57	8.76	9.51

ag) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)-propylamine (CXXII was prepared in the same way in 37% yield from the amine CXIV of Example 17r). The HCl-salt had m.p. 214° (ethanol).

$C_{21}H_{28}NO_2$.HCl (398.38)

Requires:	C 63.31	H 7.34	N 3.52	O 8.03	Cl 17.80
Found:	63.1	7.34	3.40	8.15	17.8

ah) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methyl-phenyl)propylamine (CXXIII) was prepared in the same way in 30% yield from the amine CXX of Example 19s). The HCl-salt had m.p. 240° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.94) requires:	C 69.3	H 8.31	N 3.58	Cl 9.74
Found:	69.0	8.35	3.65	9.76

ai) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxy-phenyl)propylamine (CXXIV) was prepared in the same way in 24% yield from the amine CXIX of Example 19r). M.p. >250°.

$C_{20}H_{26}ClNO_2$.HCl (384.36) requires:	C 62.50	H 7.08	N 3.65	Cl 18.45
Found:	62.5	7.09	3.63	18.4

aj) N-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine (CXXV) was obtained when the O-benzylated amine CXVI of Example 17t) was hydrogenolyzed as described in Example 9q. The hydrochloride melts at 240°.

$C_{24}H_{34}ClNO$ (388.0) requires:	C 74.29	H 8.83	N 3.61	Cl 19.14
Found:	73.9	8.90	3.52	9.48

Example 21 (continuation of Example 10)

Reduction of amides

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamine

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamide was obtained as o pale yellow oil in quantitative yield from 3-(2-methoxyphenyl)-3-phenylpropionic acid in the manner described for the amide of Example 10a). This amide (27 g, 0.08 mol) in toluene (50 g) was added dropwise under r.t. to a 3.4 M toluenic solution of SMEAH (50 g, 0,17 mol) diluted with an equal weight of toluene. The mixture was stirred at 60-70° for 2 h, cooled, treated with excess od 2N NaOH. The organic phase was separated, washed with water and extracted with 2N HCl. The acidic extract was washed with ether, basified, extracted with ether, dried and evaporated giving 17.1 g (66%) free base. This was dissolved in acetone (75 ml) and treated with 6.6 g fumaric acid dissolved in methanol, affording 20 g of the fumaric acid salt, m.p. 163-164°.

$C_{22}H_{31}ON.C_4H_4O_4$ (441.58) requires:	C 70.72	H 7.99	N 3.17	O 18.12
Found:	70.7	7.96	3.13	18.0

Example 22

Separation of (+)- and (-)-enantiomers

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen tartrate

The racemic amine (LXXXVIII of Example 9g) (48.8 g, 0.15 mol) was dissolved in 500 ml of 95% ethanol and mixed with a solution of L(+)-tartaric acid (22.5 g, 0.15 mol) in 500 ml of ethanol. The mixture was left over night at +4°. The precipitated salt was collected by filtration and washed with ethanol and ether. The yield of crude salt with $[\alpha]_{546}^{25}$ +29.5° (C 5%, methanol) was 34,3 g. Two recrystallisations from ethanol afforded 21.8 g with $[\alpha]_{546}^{25}$ +36.0°.

$C_{26}H_{37}NO_7$ requires:	C 65.66	H 7.84	N 2.95	O 23.55
Found:	65.9	8.06	2.90	23.5

(-)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen D(-)-tartrate was similarly prepared using D(-)-tartaric acid. $[\alpha]_{546}^{25}$ -35.8°.

Found:	C 65.6	H 8.00	N 2.83	O 23.6

Several of the compounds according to the invention were tested with regard to anti-cholinergic, anti-noradrenaline, and anti-calcium effects, toxicity and effect on the heart rate. The test procedures are described below, and the test results are reported in Table 1. For comparison purposes the testing also included the commercially available drug terodiline and a structurally similar compound, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, disclosed as an antidepressant in US-A-3.446.901, GB-A-1.169.944, and GB-A-1.169.945. The test results clearly show that the compounds according to the invention are superior to the known compounds especially as regards selectivity between the desired anti-cholinergic activity and the undesired side-effects.

a) Anticholinergic activity on isolated urinary bladder

Male guinea-pigs, weighing 250-350 g, were killed by a blow on the head and exsanguinated. The urinary bladders were quickly removed and placed in Na^+-Krebs, in which they were kept throughout the dissection procedure. The bladders were dissected free from adherent fat and connective tissue before they were cut open by an incision on each side from the base towards apex. The mucosa was carefully removed with a pair of scissors. Four strips, approximately 3-5 mm long were prepared by cutting in a parallel direction to the longitudinal muscle fibres, on each half of the bladder.

The bladder strips were immediately mounted vertically in 5 ml organ baths containing Na^+-Krebs solution aerated with carbogene gas to maintain the pH at about 7.4. The temperature, 37°C, was thermostatically controlled by a Lauda MS3 thermostatic circulator. The preparations were suspended between two hooks, one of which was connected to a Grass Instruments FTO3 force transducer. The isomeric tension of the preparations was recorded by a Grass polygraph model 79D. The resting tension was applied to approximately 5 mN. The strips were allowed to stabilize for at least 45 minutes. During this period the resting tension was adjusted to 5 mN and the preparations were repeatedly washed.

In the preliminary experiments concentration - effect curves for carbachol (carbamylcholin chloride) were studied, in order to determine a suitable agonist concentration for inhibition studies with antagonist. The carbachol concentration chosen, $3x10^{-6}M$, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol ($3x10^{-6}M$) every 15 minutes. The strips were washed three times after every agonist addition. This procedure was repeated until a reproducible contractant response was observed. A variation of about 10% for three subsequent contractions was accepted as reproducible.

Initially each antagonist was tested in a concentration of $10^{-6}M$, on two bladder-strips from different guinea-pigs. When a reproducible response with $3x10^{-6}M$ carbachol was obtained, the strips were incubated with the antagonist for 15 minutes before the next carbachol was added. If the antagonist produced more than 50% inhibition of the response to carbachol, a complete concentration-inhibition curve was also made. In the complete inhibition curves, the strips were then incubated for 60 minutes with a fixed concentration of the antagonist before the next addition of carbachol. The effect of the antagonists was calculated as per cent inhibition of the mean of the initial agonist-induced contractions. To generate concentration-inhibition curves the antagonists were studied in 6-8 concentrations and for each concentration a fresh preparation was used, i.e. the strips were only exposed to the antagonist once before they were discarded.

b) Antagonistic effect to noradrenaline and calcium on the portal vein

Preparation of isolated portal vein from rat

Animals: Albino, male rats, weighing about 200 g.

Bath volume: 5 ml

Buffer: Na^+-Krebs, modified by K.E. Andersson

Temperature: 37^oC

Gas: Carbogene (93.5% O_2 + 6.5% CO_2)

Muscle tension: 0.5 g

The rat is killed by a blow on the neck and decapitated. The abdomen is opened, the vein is dissected free from fat, cut open longitudinally and mounted in an organ bath. Changes in isometric tension is registered by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Noradrenaline - antagonism on portal vein

Doses: Noradrenaline $3x10^{-7}M$

The chosen doses give about 70% of maximal response. The agonist is

added to th bath at 10-minutes intervals. When r producible c ntractions are btained a fixed concentration f the t st substance is added to the bath. After an incubation p riod of 10 minutes noradrenaline is added. The n xt c nc ntration of the test substance is added when the original response of th agonist is obtained.

The antagonistic effect of the substance is calculated as per cent inhibition of the mean response by three preceding doses of the agonist.

Ca - antagonistic effect on portal vein

10 mM K^+-solution is added to the Krebs buffer to stabilize the spontaneous myogenic activity of the vein. The amplitude of the muscle contractions is measued. The test substance is added to the bath in cumulative doses until total inhibition is obtained.

c) Histamine - antagonism on isolated ileum

Preparation of isolated ileum from guinea pigs

Animals: Guinea pigs of both sexes, weighing about 350 g.
Bath volume: 5 ml
Buffer: Na^+-Krebs, modified by K.E. Andersson
Temperature: 37^oC
Gas: Carbogene (93.5% O_2 + 6.5% CO_2)
Muscle tension: 0.5 g

The guinea pig is killed by a blow on the neck and decapitated. The abdomen is opened and about 2 cm of the ileum is cut off about 15 cm above the ileocaecal junction. The piece of ileum is washed with buffer and mounted in an organ bath. Changes in isometric tension is recorded by a force displacement transducer, connected to an amplifier and a writing oscillograph.
Dose: $5x10^{-7}$ M of histamine.

The chosen dose of histamine gives about 70% of maximal response. The agonist is added to the bath at 3-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 2-10 minutes a new contraction is induced by histamine. The next concentration of the test substance is added when the original response of the agonist is obtained.

The agonistic effect of the test substance is calculated as per cent inhibition of the mean response by three preceding doses of histamine.

d) Acute toxicity in mice

The antagonists to be tested were dissolved in 0.9% NaCl. If they were not soluble in 0.9% NaCl they were diss lved in double distilled water. The solutions were prepraed on the day of the experiment.

Procedure

White male mice, 25 g, w re placed in a mouse holder. The tested compounds were given as i.v. b lus doses in one of the four tail-veins, with a volume f 0.01 ml/g mouse. Each substance concentration was given to a group of four mice. 4-5 different concentrations of the antagonists were made and tested.

The acute lethal dose (LD_{11}) was the lowest concentration of the anticholinergic drug where 4 mice of 4 tested died within 5 minutes after an i.v. bolus dose.

LD_{50}-interval: The LD_{50}-interval was between the highest dose where 4 mice survived and the lowest dose where 4 mice died within 5 minutes after an i.v. bolus dose.

e) Effect on heart rate in conscious rat

The animal is slightly anaestetized by ether and an infusion cannula is inserted into a tail vein. While still asleep the rat is placed in a simple device, made of a coarse, somewhat elastic net fixing the rat in a constant position. Electrodes are attached to the extremities and connected to an ECG-pulse pre-amplifier and a Grass polygraph. By recording the ECG, the heart rate can then be determined.

Before any substance is given the animal has regained consciousness and the heart rate has been constant for at least 15 minutes.

The substance is injected, i.v. in the infusion cannula and flushed with physiological saline.

ECG is recorded 0.25, 0.5, 1, 2, 3 and 5 minutes after completed injection and then every 5 minutes until the original heart rate is obtained.

Table I

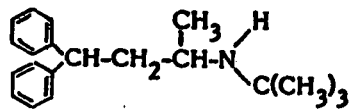
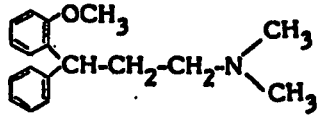
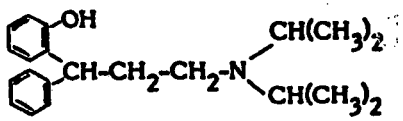
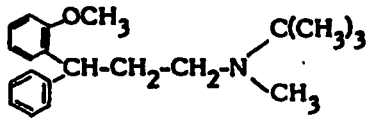
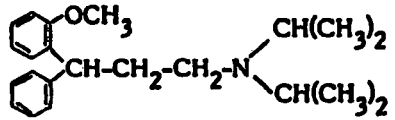
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect n heart rate threshold dose mg/kg
 Terodiline (prior art)	5.2×10^{-7}	2.4×10^{-6}	10^{-5}	4×10^{-6}	15-20	20	1-3
 GB-A-1.169.944 (antidepressant)	1.2×10^{-6}	4.4×10^{-6}	2.1×10^{-5}	3.7×10^{-7}	10-15	15	
1  Racemate	1.8×10^{-8}	10^{-5}	1.5×10^{-5}	7×10^{-6}	10-20	20	1-3
1a (+)-isomer of 1	1.8×10^{-8}						
1b (-)-isomer of 1	1.4×10^{-8}						
2 	1.5×10^{-7}	3.5×10^{-6}	9×10^{-6}		10-20	20	
3 	2.4×10^{-7}	3.6×10^{-6}	$>10^{-4}$		3-10	10	

Table I (cont.)

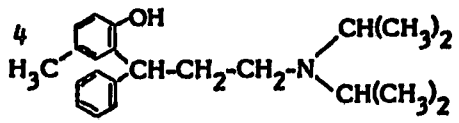
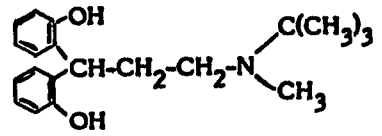
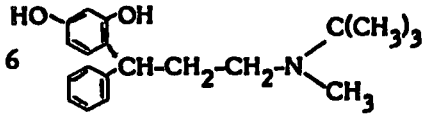
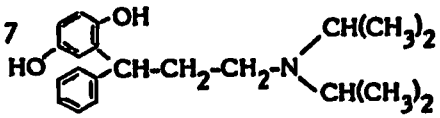
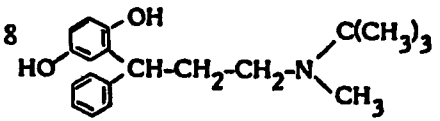
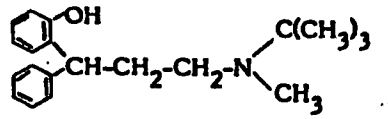
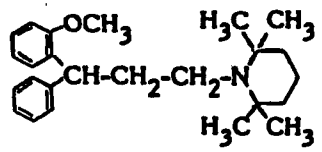
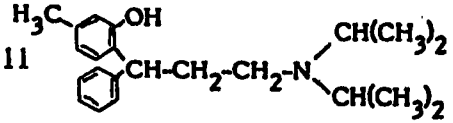
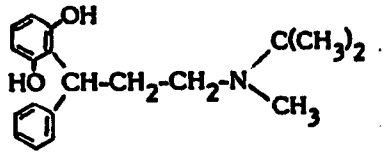
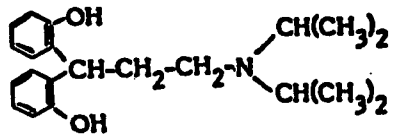
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
4 	1.5×10^{-8}	5.5×10^{-6}	6×10^{-6}	10^{-5}	30-40	40	
4a. (+)-isomer of 4 tartrate	1.3×10^{-8}		6.5×10^{-6}		10-20	20	
4b. (-)-isomer of 4 tartrate	1.3×10^{-6}		6×10^{-6}		10-20	20	
5 	4.9×10^{-9}	3.8×10^{-5}	3×10^{-5}	10^{-5}	30-45	45	1-3
6 	2.0×10^{-7}	3×10^{-5}	6.5×10^{-5}	1.3×10^{-5}	>20	>20	
7 	1.9×10^{-8}	5×10^{-5}	6.5×10^{-5}	3×10^{-6}	30-50	50	

Table I (cont.)

Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
8 	$3.1x10^{-8}$	$5x10^{-5}$	$>5x10^{-5}$	$7x10^{-6}$	>6	>6	
9 	$1.6x10^{-8}$	$5x10^{-5}$	$2.5x10^{-5}$	$1.2x10^{-6}$		20	
10 	$6.2x10^{-8}$	$4x10^{-6}$	$7x10^{-6}$	$2.5x10^{-6}$			
11 	$1.0x10^{-8}$	$5.5x10^{-6}$	10^{-5}	$2.5x10^{-6}$	10-20	20	
12 	$4.7x10^{-7}$		$2.3x10^{-5}$	$8.0x10^{-6}$	15-30	30	
13 	$9.0x10^{-9}$	$3x10^{-5}$	$1.5x10^{-5}$	$2x10^{-5}$	5-10	10	

Exampl A

Preparation f tablets

	Ingredients	mg/tablet
1.	Compound 1 in Table 1	2.0
2.	Cellulose, microcrystalline	57.0
3.	Calcium hydrogen phosphate	15.0
4.	Sodium starch glycolate	5.0
5.	Silicon dioxide, colloidal	0.25
6.	Magnesium stearate	0.75
		80.0 mg

The compound 1 according to the invention is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, the resultant mixture being mixed for about 5 minutes and then compressed into tablet form with or without filmcoating.

Example B

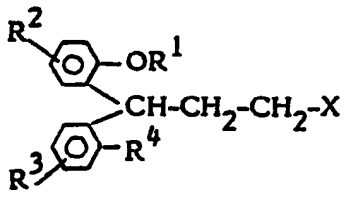
Preparation of capsules

	Ingredients	mg/capsule
1.	Compound 1 in Table 1	2
2.	Lactose	186
3.	Corn starch	20
4.	Talc	15
5.	Magnesium stearate	2
		225 mg

The compound 1 according to the invention is mixed with ingredients 2 and 3 and then milled. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

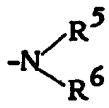
CLAIMS

1. 3,3-Diphenylpropylamin s of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



wherein R^5 and R^6 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^5 and R^6 may form a ring together with 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.

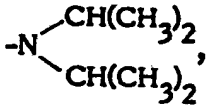
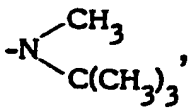
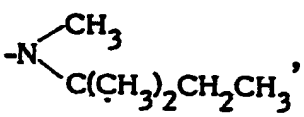
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^5 and R^6 independently signifies a saturated hydrocarbyl group, especially saturated alifatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms.

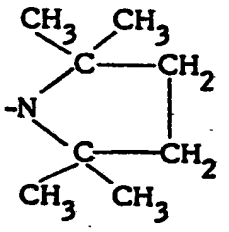
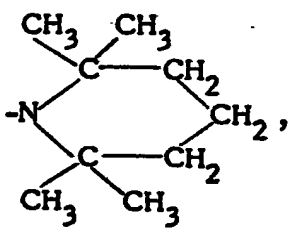
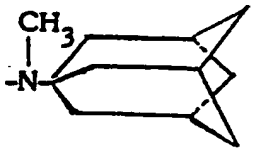
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein R^5 and R^6 taken together form a ring with the amine nitrogen.

4. 3,3-Diphenylpropylamines according to claim 1, 2 or 3, wherein R^5 and/or R^6 carries at least one hydroxy substitutent.

5. 3,3-Diphenylpropylamines according to any one of the preceeding claims, wherein at least one of R^5 and R^6 comprises a branched carbon chain.

6. 3,3-Diphenylpropylamines according to any one of claims 1-5, wherein X signifies any f the following groups a) - f), each f which may carry at least one hydroxy substituent:

a)  , b)  , c)  ,

d)  , e)  , f) 

7. 3,3-Diphenylpropylamines according to claim 1, selected from the group consisting of the following compounds, their salts with physiologically acceptable acids and, where possible, their racemates and individual enantiomers:
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine,
N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,
N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,
N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,
N-[3-(2-methoxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethylpiperidine,
(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine.

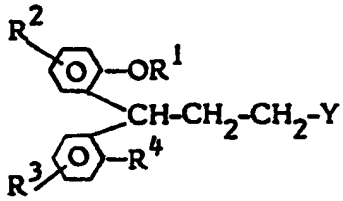
8. 3,3-Diphenylpropylamines according to any one of claims 1-7 for use as pharmaceutically active substances, especially as anticholinergic agents.

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

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

11. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1-7, comprising:

a) reacting a reactively esterified 3,3-diphenylpropan 1 of formula III



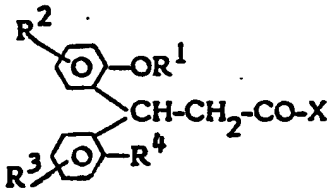
III

wherein R^1-R^4 are as defined above, any hydroxy groups may be protected and Y is a leaving group,
with an amine of formula IV

H-X IV

wherein X is as defined above, or

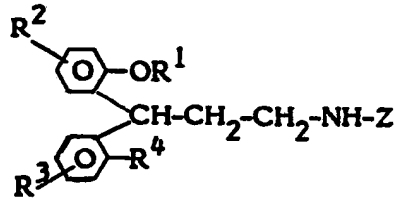
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, or

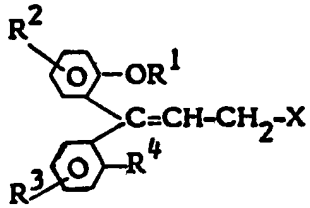
c) N-methylating a secondary 3,3-diphenylpropylamine VI



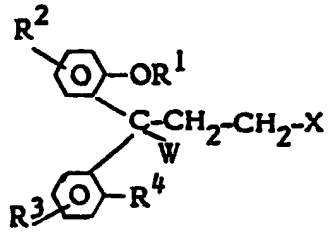
VI

wherein R^1-R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, or

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1-R^4 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, 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 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^4 is hydroxy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00016

I. CLASSIFICATION F SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

C 07 C 91/28, 93/14, A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	C 07 C 91/28, 91/30, 93/14; A 61 K 31/135
US Cl	260:568, 570.5, 571, 573; 564:316; 424:330; 514:648, 654

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

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	SE,A, 215 499 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 26 September 1976	1-11
X	DK,A, 111 894 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 21 October 1968 see page 1- page 2, line 9; the claim	1-11
X	US,A, 3 446 901 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 27 May 1969 see column 1, line 29 - line 55 & GB, 1169945	1-2, 7-11
X	GB,A, 1 169 945 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2 & US, 3446901	1-2, 7-11

.../...

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-03-30	1989 -04- 05
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Irja Berlin

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION C NTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1] partly unsearchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers ....., 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:

The expression "R^5 and R^6 may form a ring together with the amine nitrogen" (claims 1, 3, 4 and 8-11) is indefinite.

The search on claims 1, 3, 4 and 8-11 has therefore been incomplete.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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 of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] 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 claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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
X	GB, A, 1 169 944 (ED. GEISTLICH SÖHNE AG FUR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2	1-2, 7-11
X	Chemical Abstracts Vol. 97 (1982) abstract 120105n, Biol. Zh. Arm. 1982, 35(2), 101-7 (Russ).	1,3, 8-10

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

BERICHTIGTE FASSUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

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199 55 190.1 16. November 1999 (16.11.1999) DE

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.*

(48) Datum der Veröffentlichung dieser berichtigten Fassung: 21. Juni 2001

(15) Informationen zur Berichtigung:
siehe PCT Gazette Nr. 25/2001 vom 21. Juni 2001, Section II

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

(54) Bezeichnung: STABILE SALZE NEUARTIGER DERIVATE VON 3,3-DIPHENYLPROPYLAMINEN

(57) Abstract: The invention relates to highly pure, crystalline, stable compounds of 3,3-diphenylpropylamine derivatives, in the form of their salts, a method for their production and highly pure, stable, intermediate products. The method is particularly characterized by regio- and chemo-selectivity and high yields and provides salts of phenolic monoesters of 3,3-diphenylpropylamines, which are particularly suitable for application in technical pharmaceutic formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrogenfumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate hydrochloride hydrate. The method further provides essential, stable, crystalline intermediate products for the production of the above salts. A preferred intermediate product is *R*-(-)-3-(3-diisopropylaminophenylpropyl)-4-hydroxybenzoic acid methyl ester.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft hochreine, kristalline, stabile Verbindungen neuartiger Derivate von 3,3-Diphenylpropylaminen in Form ihrer Salze, Verfahren zu deren Herstellung sowie hochreine, stabile Zwischenprodukte. Insbesondere zeichnet sich das Verfahren durch Regio- und Chemoselektivität sowie hohe Ausbeute aus. Es werden Salze phenolischer Monoester von 3,3-Diphenylpropylaminen zur Verfügung gestellt, die sich besonders gut zum Einsatz in pharmazeutisch-technischen Formulierungen eignen. Bevorzugte Verbindungen sind *R*-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrogenfumarat und*R*-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat. Weiterhin werden stabile, kristalline verfahrenswesentliche Zwischenprodukte zum Erhalt der vorgenannten Salze zur Verfügung gestellt. Ein bevorzugtes Zwischenprodukt ist *R*-(-)-3-(3-Diisopropylamino-phenyl-propyl)-4-hydroxy-benzoesäuremethylester.

WO 01/35957 A2

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

PCT

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

(Artikel 36 und Regel 70 PCT)

Aktenzeichen des Anmelders oder Anwalts	**WEITERES VORGEHEN** siehe Mitteilung über die Übersendung des internationalen vorläufigen Prüfungsberichts (Formblatt PCT/IPEA/416)	
11012/um		
Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Prioritätsdatum *(Tag/Monat/Tag)*
PCT/EP00/11309	15/11/2000	16/11/1999
Internationale Patentklassifikation (IPK) oder nationale Klassifikation und IPK C07C215/54		
Anmelder SCHWARZ PHARMA AG et al.		

1. Dieser internationale vorläufige Prüfungsbericht wurde von der mit der internationalen vorläufigen Prüfung beauftragten Behörde erstellt und wird dem Anmelder gemäß Artikel 36 übermittelt.

2. Dieser BERICHT umfaßt insgesamt 5 Blätter einschließlich dieses Deckblatts.

   ☒ Außerdem liegen dem Bericht ANLAGEN bei; dabei handelt es sich um Blätter mit Beschreibungen, Ansprüchen und/oder Zeichnungen, die geändert wurden und diesem Bericht zugrunde liegen, und/oder Blätter mit vor dieser Behörde vorgenommenen Berichtigungen (siehe Regel 70.16 und Abschnitt 607 der Verwaltungsrichtlinien zum PCT).

   Diese Anlagen umfassen insgesamt 5 Blätter.

3. Dieser Bericht enthält Angaben zu folgenden Punkten:

   - I ☒ Grundlage des Berichts
   - II ☐ Priorität
   - III ☐ Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
   - IV ☐ Mangelnde Einheitlichkeit der Erfindung
   - V ☒ Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
   - VI ☐ Bestimmte angeführte Unterlagen
   - VII ☐ Bestimmte Mängel der internationalen Anmeldung
   - VIII ☐ Bestimmte Bemerkungen zur internationalen Anmeldung

Datum der Einreichung des Antrags	Datum der Fertigstellung dieses Berichts
17/01/2001	07.03.2002
Name und Postanschrift der mit der internationalen vorläufigen Prüfung beauftragten Behörde: Europäisches Patentamt D-80298 München Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bevollmächtigter Bediensteter Goetz, G Tel. Nr. +49 89 2399 8105

Formblatt PCT/IPEA/409 (Deckblatt) (Januar 1994)

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

Internationales Aktenzeichen PCT/EP00/11309

I. Grundlage des Berichts

1. Hinsichtlich der **Bestandteile** der internationalen Anmeldung (*Ersatzblätter, die dem Anmeldeamt auf eine Aufforderung nach Artikel 14 hin vorgelegt wurden, gelten im Rahmen dieses Berichts als "ursprünglich eingereicht" und sind ihm nicht beigefügt, weil sie keine Änderungen enthalten (Regeln 70.16 und 70.17)*):

Beschreibung, Seiten:

1-44	ursprüngliche Fassung				

Patentansprüche, Nr.:

1-15,16 (Teil),29, 30	ursprüngliche Fassung				
16 (Teil),17-28	eingegangen am	05/10/2001	mit Schreiben vom	05/10/2001	

Zeichnungen, Blätter:

1/1	ursprüngliche Fassung				

2. Hinsichtlich der **Sprache**: Alle vorstehend genannten Bestandteile standen der Behörde in der Sprache, in der die internationale Anmeldung eingereicht worden ist, zur Verfügung oder wurden in dieser eingereicht, sofern unter diesem Punkt nichts anderes angegeben ist.

   Die Bestandteile standen der Behörde in der Sprache: zur Verfügung bzw. wurden in dieser Sprache eingereicht; dabei handelt es sich um

   ☐ die Sprache der Übersetzung, die für die Zwecke der internationalen Recherche eingereicht worden ist (nach Regel 23.1(b)).

   ☐ die Veröffentlichungssprache der internationalen Anmeldung (nach Regel 48.3(b)).

   ☐ die Sprache der Übersetzung, die für die Zwecke der internationalen vorläufigen Prüfung eingereicht worden ist (nach Regel 55.2 und/oder 55.3).

3. Hinsichtlich der in der internationalen Anmeldung offenbarten **Nucleotid- und/oder Aminosäuresequenz** ist die internationale vorläufige Prüfung auf der Grundlage des Sequenzprotokolls durchgeführt worden, das:

   ☐ in der internationalen Anmeldung in schriftlicher Form enthalten ist.

   ☐ zusammen mit der internationalen Anmeldung in computerlesbarer Form eingereicht worden ist.

   ☐ bei der Behörde nachträglich in schriftlicher Form eingereicht worden ist.

   ☐ bei der Behörde nachträglich in computerlesbarer Form eingereicht worden ist.

   ☐ Die Erklärung, daß das nachträglich eingereichte schriftliche Sequenzprotokoll nicht über den Offenbarungsgehalt der internationalen Anmeldung im Anmeldezeitpunkt hinausgeht, wurde vorgelegt.

   ☐ Die Erklärung, daß die in computerlesbarer Form erfassten Informationen dem schriftlichen

Sequenzprotokoll entsprechen, wurde vorgelegt.

4. Aufgrund der Änderungen sind folgende Unterlagen fortgefallen:

   ☐ Beschreibung, Seiten:
   ☐ Ansprüche, Nr.:
   ☐ Zeichnungen, Blatt:

5. ☐ Dieser Bericht ist ohne Berücksichtigung (von einigen) der Änderungen erstellt worden, da diese aus den angegebenen Gründen nach Auffassung der Behörde über den Offenbarungsgehalt in der ursprünglich eingereichten Fassung hinausgehen (Regel 70.2(c)).

   (Auf Ersatzblätter, die solche Änderungen enthalten, ist unter Punkt 1 hinzuweisen;sie sind diesem Bericht beizufügen).

6. Etwaige zusätzliche Bemerkungen:

V. Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigk it und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1. Feststellung

Neuheit (N)	Ja:	Ansprüche	1-7,8-17,21,22,26,27-30
	Nein:	Ansprüche	18-20,23-25
Erfinderische Tätigkeit (ET)	Ja:	Ansprüche	1-7,8-17
	Nein:	Ansprüche	21,22,27-30
Gewerbliche Anwendbarkeit (GA)	Ja:	Ansprüche	1-30
	Nein:	Ansprüche	

2. Unterlagen und Erklärungen
   siehe Beiblatt

Zu Punkt V

Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

D1: WO 98 43942 A (HARALDSSON MARTIN ;PHARMACIA & UPJOHN AB (SE); RINGBERG ERIK (SE);) 8. Oktober 1998 (1998-10-08)
D2: WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26. Mai 1994 (1994-05-26)
D3: PALMER, L. ET AL.: 'Determination of tolterodine and the 5-hydroxymetylmetabolite ...' J. PHARM. BIOMED. ANAL., Bd. 16, 1997, Seiten 155-165, XP000995770

Es ist darauf hinzuweisen, dass die Reinheit und Stabilität eines Stoffes einer an sich bekannten Verbindung keine Neuheit verleihen.

1. D1 offenbart die Zwischenprodukte gemäß der Ansprüche 19 und 24 (s. D1: Seite 76, Zeilen 7-8).
   Desweiteren offenbart D1 die Zwischenprodukte gemäß der Ansprüche 20 und 25 (s. D1: Seite 36, Zeilen 32-33).

2. D2 offenbart die Zwischenprodukte gemäß der Ansprüche 18 und 23 (s. D2: Seite 12, Zeilen 15-16).

3. D3 offenbart das Zwischenprodukt gemäß der Anspruch 20 (s. D3: Abbildung 1).

4. Damit sind die Ansprüche 18,19,20,23,24,25 nicht mehr neu.
   Da D1 und D2 die Verwendung dieser Zwischenprodukte zur Herstellung von Wirkstoffen offenbart sind die Ansprüche 21 und 27 ebenfalls nicht mehr neu. (Artikel 33.2 PCT).

5. Ansprüche 1-7, 8-17
   Die beanspruchten Verbindungen sind im Stand der Technik nicht beschrieben. Damit sind diese Ansprüche sowie die Ansprüche 8-17 (Herstellung dieser

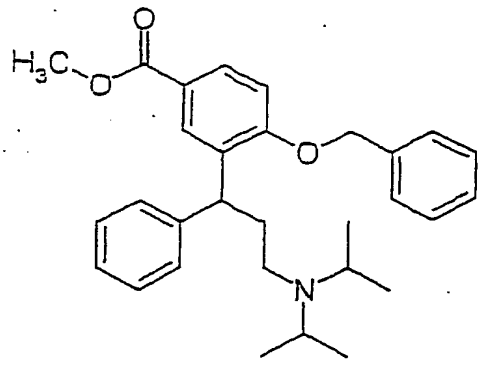
Verbindungen) neu.
Die beanspruchten Verbindungen zeichnen sich durch eine hohe Reinheit und Kristallstruktur aus. Diese kristallinen Verbindungen sind sehr stabil und lagerungsbeständig und zeichnen sich durch gute pharmakokinetische Eigenschaften aus.
Diese Vorteile waren durch den Stand der Technik nicht vorhersehbar und sind als überraschend zu werten.

6. Ansprüche 21,22,27-30:
Da die beanspruchten Zwischenverbindungen gemäß der Ansprüche 18 bis 20 und 23 bis 25 nicht neu sind kann auch deren Verwendung als Zwischenprodukt als nicht erfinderisch angesehen werden

setzt werden.

17. Verfahren nach Ansprüchen 10 bis 13 zur Herstellung von R-(+)-2-(3-Diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobuttersäureester Hydrochlorid Hydrat, dadurch gekennzeichnet, daß die phenolische Veresterung von R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) ohne Zusatz einer externen Base durchgeführt wird, indem Lösungen von (6) in Lösungen von Isobuttersäurechlorid, die mindestens 1 Moläquivalent Wasser enthalten, zugetropft werden, um direkt ein entsprechendes stabiles, hydrathaltiges Hydrochlorid zu erhalten.

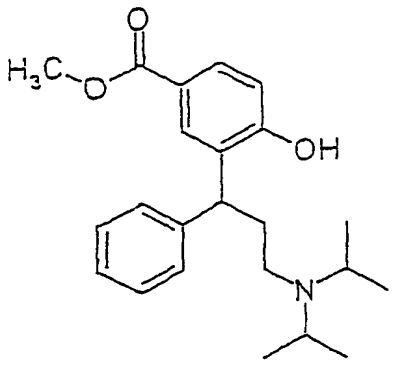
18. Verbindung der Formel III



Formel III

in hochreiner, kristalliner und stabiler Form.

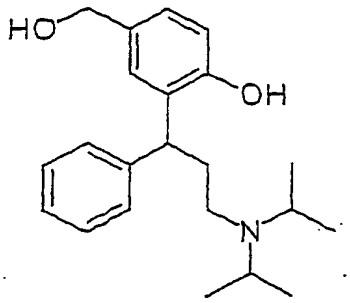
19. Verbindung der Formel V



Formel V

in hochreiner, kristalliner, und stabiler Form.

20. Verbindung der Formel VI



Formel VI

in hochreiner, kristalliner, und stabiler Form.

21. Verwendung einer Verbindung nach Ansprüchen 18 bis 20 als hochreines, kristallines, stabiles Zwischenprodukt bei der Herstellung von pharmazeutisch nützlichen Verbindungen der Formel I nach Patentanspruch 1.

22. Verwendung einer Verbindung nach Ansprüchen 18 bis 20 als Zwischenprodukt bei der Herstellung von phenolischen Monoestern der allgemeinen Formel A