Practitioner's Docket No. 55647-C (45107) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Mail Stop: Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s): Claus Meese and Bengt Sparf

WARNING: *37 CFR 1.41(a)(1) points out:*

"(a) A patent is applied for in the name or names of the actual inventor or inventors.

(1) The inventorship of a nonprovisional application is that inventorship set forth in the oath or declaration as prescribed by § 1.63, except as provided for in § 1.53(d)(4) and § 1.63(d). If an oath or declaration as prescribed by § 1.63 is not filed during the pendency of a nonprovisional application, the inventorship is that inventorship set forth in the application papers filed pursuant to § 1.53(b), unless a petition under this paragraph accompanied by the fee set forth in § 1.17(i) is filed supplying or changing the name or names of the inventor or inventors."

For (title): NOVEL DERIVATIVES OF 3, 3-DEPHENYLPROPYLAMINES

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date **January 27, 2004**, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EV 342587673 US addressed to the: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Elena Misiaszek
(type or print name of person mailing paper)

Elena Misiaszek
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

WARNING:* *Each paper or fee filed by "Express Mail" **must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442*

1. Type of Application

This new application is for a(n)

(check one applicable item below)

[X] Original (nonprovisional)

[ ] Design

[ ] Plant

WARNING: ***Do not*** *use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4), unless the International Application is being filed as a divisional, continuation or continuation-in-part application.*

WARNING: ***Do not*** *use this transmittal for the filing of a provisional application.*

NOTE: If one of the following 3 items apply, then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED and a NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION.

[ ] Divisional.

[X] Continuation.

[ ] Continuation-in-part (C-I-P).

2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

NOTE: A nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications or copending international applications designating the United States of America. In order for a nonprovisional application to claim the benefit of a prior filed copending nonprovisional application or copending international application designating the United States of America, each prior application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. Each prior application must also be:

(i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or

(ii) Complete as set forth in § 1.51(b); or

(iii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and include the basic filing fee set forth in § 1.16; or

(iv) Entitled to a filing date as set forth in § 1.53(b) and have paid therein the processing and retention fee set forth in § 1.21(l) within the time period set forth in § 1.53(f).

37 CFR 1.78(a)(1).

NOTE *If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional application is claimed, then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

WARNING: *If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. 120, 121 or 365(c). (35 U.S.C. 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.*

WARNING: *When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional application* ***must*** *be filed prior to the Saturday, Sunday, or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).*

[X] The new application being transmitted claims the benefit of prior U.S. application(s). Enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

3. Papers Enclosed

A. Required for Filing Date under 37 C.F.R. 1.53(b) (Regular) or 37 C.F.R. 1.153 (Design) Application

94 Pages of Specification
24 Pages of Claims
1 Sheets of Drawing
[X] Formal
[ ] Informal

B. Other Papers Enclosed

1 Pages of Abstract
2 Other: International Search Report

WARNING: ***DO NOT*** *submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. For comments on proposed then-new 37 C.F.R. 1.84, see Notice of March 9, 1988 . . . (1990 O.G. 57-62).*

NOTE: *"Identifying indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (5/8 inch) down from the top of the page." 37 C.F.R. 1.84(c)).*

(complete the following, if applicable)

[ ] The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)." 37 C.F.R. 1.84(b).

4. Additional Papers Enclosed

[x] Preliminary Amendment
[ ] Information Disclosure Statement (37 C.F.R. 1.98)
[ ] Form PTO-1449
[ ] Citations
[ ] Declaration of Biological Deposit
[ ] Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
[ ] Authorization of Attorney(s) to Accept and Follow Instructions from Representative
[ ] Special Comments
[ ] Other:

5. Declaration or Oath

NOTE: A newly executed declaration is not required in a continuation or divisional application provided the prior nonprovisional application contained a declaration as required, the application being filed is by all or fewer than all the inventors named in the prior application, there is no new matter in the application being filed, and a copy of the executed declaration filed in the prior application (showing the signature or an indication thereon that it was signed) is submitted. The copy must be accompanied by a statement requesting deletion of the names of person(s) who are not inventors of the application being filed. If the declaration in the prior application was filed under § 1.47 then a copy of that declaration must be filed accompanied by a copy of the decision granting § 1.47 status or, if a nonsigning person under § 1.47 has subsequently joined in a prior application, then a copy of the subsequently executed declaration must be filed. See 37 CFR 1.63(d).

NOTE: A declaration filed to complete an application must be executed, identify the specification to which it is directed, identify each inventor by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and the residence, post office address and country of citizenship of each inventor and state whether the inventor is a sole or joint inventor. 37 CFR 1.63(a)(1)-(4).

[X] Enclosed

Executed by

(check **all** *applicable boxes)*

[X] inventor(s) **(COPY FROM PARENT APPLICATION)**
[ ] legal representative of inventor(s). 37 CFR 1.42 or 1.43.
[ ] joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
  [ ] This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. See item 13 below for fee.

[ ] Not Enclosed.

NOTE: *Where the filing is a completion in the U.S. of an International Application, or where the completion of the U.S. application contains subject matter in addition to the International Application, the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

[ ] Application is made by a person authorized under 37 C.F.R. 1.41(c) on behalf of *all* the above named inventor(s).

(The declaration or oath, along with the surcharge required by 37 CFR 1.16(e), can be filed subsequently).

NOTE: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).

[ ] Showing that the filing is authorized.
(not required unless called into question. 37 CFR 1.41(d))

6. Inventorship Statement

WARNING: If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.

The inventorship for all the claims in this application are:

[ ] The same.

or

[ ] Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,
[ ] is submitted.
[ ] will be submitted.

7. Language

NOTE: An application including a signed oath or declaration may be filed in a language other than English. An English translation of the non-English language application and the processing fee of $130.00 required by 37 CFR 1.17(k) is required to be filed with the application, or within such time as may be set by the Office. 37 CFR 1.52(d).

[X] English
[ ] Non-English
[ ] The attached translation includes a statement that the translation is accurate. 37 C.F.R. 1.52(d).

8. Assignment

[X] An assignment of the invention to Schwarz Pharma AG

[ ] is attached. A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

[X] was filed in the parent application (copy enclosed)
[ ] will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters-one for the application and one for the assignment" Notice of May 4, 1990 (1114 O.G. 77-78).

WARNING: *A newly executed "STATEMENT UNDER 37 CFR 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-64.*

9. Certified Copy

Certified copy(ies) of application(s)

Country	Appln. No.	Filed
Europe	98 108608.5	5/12/98

from which priority is claimed

[ ] is enclosed.
[X] was filed in parent.
[ ] will follow.

NOTE: *The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63.*

NOTE: *This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application, then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

10. Fee Calculation (37 C.F.R. 1.16)

A. [X] Regular application

CLAIMS AS FILED

Claims	Number Filed	Basic Fee Allowance	Number Extra	Rate	Basic Fee 37 C.F.R. 1.16(a) $770.00
Total Claims (37 CFR 1.16(c))	89	- 20 =	69	x $ 18.00	$1242
Independent Claims (37 CFR 1.16(b))	5	- 3 =	2	x $86.00	$172
Multiple Dependent Claim(s), if any (37 CFR 1.16(d))			+	$290.00	$290

[ ] Amendment cancelling extra claims is enclosed.
[ ] Amendment deleting multiple-dependencies is enclosed.
[ ] Fee for extra claims is not being paid at this time.

NOTE: *If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).*

Filing Fee Calculation $ 2474.00

B. [ ] Design application
($330.00—37 CFR 1.16(f))

Filing Fee Calculation $_____

C. [ ] Plant application
($540.00—37 CFR 1.16(g))

Filing Fee Calculation $ _____

11. Small Entity Statement(s)

[ ] Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is (are) attached.

WARNING: *"Status as a small entity must be specifically established in each application or patent in which the status is available and desired. Status as a small entity in one application or patent does not affect any other application or patent, including applications or patents which are directly or indirectly dependent upon the application or patent in which the status has been established. The refiling of an application under § 1.53 as a continuation, division, or continuation-in-part (including a continued prosecution application under § 1.53(d)), or the filing of a reissue application requires a new determination as to continued entitlement to small entity status for the continuing or reissue application. A nonprovisional application claiming benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) of a prior application, or a reissue application may rely on a statement filed in the prior application or in the patent if the nonprovisional application or the reissue application includes a reference to the statement in the prior application or in the patent or includes a copy of the statement in the prior application or in the patent and status as a small entity is still proper and desired. The payment of the small entity basic statutory filing fee will be treated as such a reference for purposes of this section." 37 CFR 1.28(a)(2).*

(complete the following, if applicable)

[ ] Status as a small entity was claimed in prior application _____, filed on_____ _____ from which benefit is being claimed for this application under:

35 U.S.C. § [ ] 119(e),
[ ] 120,
[ ] 121,
[ ] 365(c),

and which status as a small entity is still proper and desired.

[ ] A copy of the statement in the prior application is included.

Filing Fee Calculation (50% of **A**, **B** or **C** above) $_____

NOTE: *Any excess of the full fee paid will be refunded if a small entity status is established refund request are filed within 2 months of the date of timely payment of a full fee. The two-month period is not extendable under § 1.136. 37 CFR 1.28(a).*

12. Request for International-Type Search (37 C.F.R. 1.104(d))

(complete, if applicable)

[ ] Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. Fee Payment Being Made at This Time

[ ] Not Enclosed

[ ] No filing fee is to be paid at this time.
(This and the surcharge required by 37 C.F.R. 1.16(e) can be paid subsequently.)

[X] Enclosed

[X]	Filing fee	$ 2474.00
[ ]	Recording assignment ($40.00; 37 C.F.R. 1.21(h)) (See attached "COVER SHEET FOR ASSIGNMENT ACCOMPANYING NEW APPLICATION.")	$
[ ]	Petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached ($130.00; 37 C.F.R. 1.47 and 1.17(i))	$
[ ]	For processing an application with a specification in a non-English language ($130.00; 37 C.F.R. 1.52(d) and 1.17(k))	$
[ ]	Processing and retention fee ($130.00; 37 C.F.R. 1.53(d) and 1.21(l))	$
[ ]	Fee for international-type search report ($40.00; 37 C.F.R. 1.21(e))	$

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application that is abandoned for failing to complete the application pursuant to 37 CFR 1.53(f) and this, as well as the changes to 37 CFR 1.53 and 1.78(a)(1), indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid, or the processing and retention fee of § 1.21(l) must be paid, within 1 year from notification under § 53(f).

Total Fees Enclosed $ 2474.00

14. Method of Payment of Fees

[X] Check in the amount of $ 2474.00

[ ] Charge Account No. _____ in the amount of $_____.
A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

15. Authorization to Charge Additional Fees

WARNING: *If no fees are to be paid on filing, the following items should not be completed.*

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.*

[X] The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. **04-1105.**
- [X] 37 C.F.R. 1.16(a), (f) or (g) (filing fees)
- [X] 37 C.F.R. 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

- [X] 37 C.F.R. 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)
- [X] 37 CFR 1.17(a)(1)-(5) (extension fees pursuant to § 1.136(a).
- [X] 37 C.F.R. 1.17 (application processing fees)

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 CFR 1.136(a)(3).

- [ ] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b)).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying, . . issue fee." From the wording of 37 CFR 1.28(b), (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

16. Instructions as to Overpayment

NOTE: ". . . Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 CFR 1.26(a).

[X] Credit Account No. 04-1105.

[ ] Refund

Chris C. O'Day

Date: 1-27-04 **SIGNATURE OF PRACTITIONER**

Reg. No. 38,256 Christine C. O'Day

(type or print name of practitioner)

EDWARDS & ANGELL, LLP

Tel. No.: (617) 439-4444 P.O. Box 9169

P.O. Address

Customer No.: 21874 Boston, MA 02209

[X] **Incorporation by reference of added pages**

(check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED)

[ ] Plus Added Pages for New Application Transmittal Where Benefit of Prior U.S. Application(s) Claimed

Number of pages added _____

[ ] Plus Added Pages for Papers Referred to in Item 5 Above

Number of pages added 2

[ ] Plus added pages deleting names of inventor(s) named on prior application(s) who is/are no longer inventor(s) of the subject matter claimed in this application.

Number of pages added _____

[ ] Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added _____

[ ] **Statement Where No Further Pages Added**

(if no further pages form a part of this Transmittal, then end this Transmittal with this page and check the following item)

[X] This transmittal ends with this page.

431497

Practitioner's Docket No. 55647-C (45107) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Mail Stop: Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s): Claus Meese and Bengt Sparf

WARNING: *37 CFR 1.41(a)(1) points out:*

"(a) A patent is applied for in the name or names of the actual inventor or inventors.

(1) The inventorship of a nonprovisional application is that inventorship set forth in the oath or declaration as prescribed by § 1.63, except as provided for in § 1.53(d)(4) and § 1.63(d). If an oath or declaration as prescribed by § 1.63 is not filed during the pendency of a nonprovisional application, the inventorship is that inventorship set forth in the application papers filed pursuant to § 1.53(b), unless a petition under this paragraph accompanied by the fee set forth in § 1.17(i) is filed supplying or changing the name or names of the inventor or inventors."

For (title): NOVEL DERIVATIVES OF 3, 3-DEPHENYLPROPYLAMINES

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date **January 27, 2004**, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EV 342587673 US addressed to the: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Elena Misiaszek
(type or print name of person mailing paper)

Elena Misiaszek
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

WARNING:* *Each paper or fee filed by "Express Mail" **must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442*

1. Type of Application

This new application is for a(n)

(check one applicable item below)

[X] Original (nonprovisional)

[ ] Design

[ ] Plant

WARNING: ***Do not*** *use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4), unless the International Application is being filed as a divisional, continuation or continuation-in-part application.*

WARNING: ***Do not*** *use this transmittal for the filing of a provisional application.*

NOTE: If one of the following 3 items apply, then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED and a NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION.

[ ] Divisional.

[X] Continuation.

[ ] Continuation-in-part (C-I-P).

2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

NOTE: A nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications or copending international applications designating the United States of America. In order for a nonprovisional application to claim the benefit of a prior filed copending nonprovisional application or copending international application designating the United States of America, each prior application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. Each prior application must also be:

(i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or

(ii) Complete as set forth in § 1.51(b); or

(iii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and include the basic filing fee set forth in § 1.16; or

(iv) Entitled to a filing date as set forth in § 1.53(b) and have paid therein the processing and retention fee set forth in § 1.21(l) within the time period set forth in § 1.53(f).

37 CFR 1.78(a)(1).

NOTE *If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional application is claimed, then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

WARNING: *If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. 120, 121 or 365(c). (35 U.S.C. 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.*

WARNING: *When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional application* ***must*** *be filed prior to the Saturday, Sunday, or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).*

[X] The new application being transmitted claims the benefit of prior U.S. application(s). Enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

3. Papers Enclosed

A. Required for Filing Date under 37 C.F.R. 1.53(b) (Regular) or 37 C.F.R. 1.153 (Design) Application

94 Pages of Specification
24 Pages of Claims
1 Sheets of Drawing
[X] Formal
[ ] Informal

B. Other Papers Enclosed

1 Pages of Abstract
2 Other: International Search Report

WARNING: ***DO NOT*** *submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. For comments on proposed then-new 37 C.F.R. 1.84, see Notice of March 9, 1988 . . . (1990 O.G. 57-62).*

NOTE: *"Identifying indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (5/8 inch) down from the top of the page." 37 C.F.R. 1.84(c)).*

(complete the following, if applicable)

[ ] The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)." 37 C.F.R. 1.84(b).

4. Additional Papers Enclosed

[x] Preliminary Amendment
[ ] Information Disclosure Statement (37 C.F.R. 1.98)
[ ] Form PTO-1449
[ ] Citations
[ ] Declaration of Biological Deposit
[ ] Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
[ ] Authorization of Attorney(s) to Accept and Follow Instructions from Representative
[ ] Special Comments
[ ] Other:

5. Declaration or Oath

NOTE: A newly executed declaration is not required in a continuation or divisional application provided the prior nonprovisional application contained a declaration as required, the application being filed is by all or fewer than all the inventors named in the prior application, there is no new matter in the application being filed, and a copy of the executed declaration filed in the prior application (showing the signature or an indication thereon that it was signed) is submitted. The copy must be accompanied by a statement requesting deletion of the names of person(s) who are not inventors of the application being filed. If the declaration in the prior application was filed under § 1.47 then a copy of that declaration must be filed accompanied by a copy of the decision granting § 1.47 status or, if a nonsigning person under § 1.47 has subsequently joined in a prior application, then a copy of the subsequently executed declaration must be filed. See 37 CFR 1.63(d).

NOTE: A declaration filed to complete an application must be executed, identify the specification to which it is directed, identify each inventor by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and the residence, post office address and country of citizenship of each inventor and state whether the inventor is a sole or joint inventor. 37 CFR 1.63(a)(1)-(4).

[X] Enclosed

Executed by

(check **all** *applicable boxes)*

[X] inventor(s) **(COPY FROM PARENT APPLICATION)**
[ ] legal representative of inventor(s). 37 CFR 1.42 or 1.43.
[ ] joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
  [ ] This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. See item 13 below for fee.

[ ] Not Enclosed.

NOTE: *Where the filing is a completion in the U.S. of an International Application, or where the completion of the U.S. application contains subject matter in addition to the International Application, the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

[ ] Application is made by a person authorized under 37 C.F.R. 1.41(c) on behalf of *all* the above named inventor(s).

(The declaration or oath, along with the surcharge required by 37 CFR 1.16(e), can be filed subsequently).

NOTE: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).

[ ] Showing that the filing is authorized.
(not required unless called into question. 37 CFR 1.41(d))

6. Inventorship Statement

WARNING: If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.

The inventorship for all the claims in this application are:

[ ] The same.

or

[ ] Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,
[ ] is submitted.
[ ] will be submitted.

7. Language

NOTE: An application including a signed oath or declaration may be filed in a language other than English. An English translation of the non-English language application and the processing fee of $130.00 required by 37 CFR 1.17(k) is required to be filed with the application, or within such time as may be set by the Office. 37 CFR 1.52(d).

[X] English
[ ] Non-English
[ ] The attached translation includes a statement that the translation is accurate. 37 C.F.R. 1.52(d).

8. Assignment

[X] An assignment of the invention to Schwarz Pharma AG

[ ] is attached. A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

[X] was filed in the parent application (copy enclosed)
[ ] will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters-one for the application and one for the assignment" Notice of May 4, 1990 (1114 O.G. 77-78).

WARNING: *A newly executed "STATEMENT UNDER 37 CFR 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-64.*

9. Certified Copy

Certified copy(ies) of application(s)

Country	Appln. No.	Filed
Europe	98 108608.5	5/12/98

from which priority is claimed

[ ] is enclosed.
[X] was filed in parent.
[ ] will follow.

NOTE: *The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63.*

NOTE: *This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application, then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

10. Fee Calculation (37 C.F.R. 1.16)

A. [X] Regular application

CLAIMS AS FILED

Claims	Number Filed	Basic Fee Allowance	Number Extra	Rate	Basic Fee 37 C.F.R. 1.16(a) $770.00
Total Claims (37 CFR 1.16(c))	89	- 20 =	69	x $ 18.00	$1242
Independent Claims (37 CFR 1.16(b))	5	- 3 =	2	x $86.00	$172
Multiple Dependent Claim(s), if any (37 CFR 1.16(d))			+	$290.00	$290

[ ] Amendment cancelling extra claims is enclosed.
[ ] Amendment deleting multiple-dependencies is enclosed.
[ ] Fee for extra claims is not being paid at this time.

NOTE: *If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).*

Filing Fee Calculation $ 2474.00

B. [ ] Design application
($330.00—37 CFR 1.16(f))

Filing Fee Calculation $_____

C. [ ] Plant application
($540.00—37 CFR 1.16(g))

Filing Fee Calculation $ _____

11. Small Entity Statement(s)

[ ] Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is (are) attached.

WARNING: *"Status as a small entity must be specifically established in each application or patent in which the status is available and desired. Status as a small entity in one application or patent does not affect any other application or patent, including applications or patents which are directly or indirectly dependent upon the application or patent in which the status has been established. The refiling of an application under § 1.53 as a continuation, division, or continuation-in-part (including a continued prosecution application under § 1.53(d)), or the filing of a reissue application requires a new determination as to continued entitlement to small entity status for the continuing or reissue application. A nonprovisional application claiming benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) of a prior application, or a reissue application may rely on a statement filed in the prior application or in the patent if the nonprovisional application or the reissue application includes a reference to the statement in the prior application or in the patent or includes a copy of the statement in the prior application or in the patent and status as a small entity is still proper and desired. The payment of the small entity basic statutory filing fee will be treated as such a reference for purposes of this section." 37 CFR 1.28(a)(2).*

(complete the following, if applicable)

[ ] Status as a small entity was claimed in prior application _____, filed on_____ _____ from which benefit is being claimed for this application under:

35 U.S.C. § [ ] 119(e),
[ ] 120,
[ ] 121,
[ ] 365(c),

and which status as a small entity is still proper and desired.

[ ] A copy of the statement in the prior application is included.

Filing Fee Calculation (50% of **A**, **B** or **C** above) $_____

NOTE: *Any excess of the full fee paid will be refunded if a small entity status is established refund request are filed within 2 months of the date of timely payment of a full fee. The two-month period is not extendable under § 1.136. 37 CFR 1.28(a).*

12. Request for International-Type Search (37 C.F.R. 1.104(d))

(complete, if applicable)

[ ] Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. Fee Payment Being Made at This Time

[ ] Not Enclosed

[ ] No filing fee is to be paid at this time.
(This and the surcharge required by 37 C.F.R. 1.16(e) can be paid subsequently.)

[X] Enclosed

[X]	Filing fee	$ 2474.00
[ ]	Recording assignment ($40.00; 37 C.F.R. 1.21(h)) (See attached "COVER SHEET FOR ASSIGNMENT ACCOMPANYING NEW APPLICATION.")	$
[ ]	Petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached ($130.00; 37 C.F.R. 1.47 and 1.17(i))	$
[ ]	For processing an application with a specification in a non-English language ($130.00; 37 C.F.R. 1.52(d) and 1.17(k))	$
[ ]	Processing and retention fee ($130.00; 37 C.F.R. 1.53(d) and 1.21(l))	$
[ ]	Fee for international-type search report ($40.00; 37 C.F.R. 1.21(e))	$

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application that is abandoned for failing to complete the application pursuant to 37 CFR 1.53(f) and this, as well as the changes to 37 CFR 1.53 and 1.78(a)(1), indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid, or the processing and retention fee of § 1.21(l) must be paid, within 1 year from notification under § 53(f).

Total Fees Enclosed $ 2474.00

14. Method of Payment of Fees

[X] Check in the amount of $ 2474.00

[ ] Charge Account No. _____ in the amount of $_____.
A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

15. Authorization to Charge Additional Fees

WARNING: *If no fees are to be paid on filing, the following items should not be completed.*

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.*

[X] The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. **04-1105.**
- [X] 37 C.F.R. 1.16(a), (f) or (g) (filing fees)
- [X] 37 C.F.R. 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

- [X] 37 C.F.R. 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)
- [X] 37 CFR 1.17(a)(1)-(5) (extension fees pursuant to § 1.136(a).
- [X] 37 C.F.R. 1.17 (application processing fees)

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 CFR 1.136(a)(3).

- [ ] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b)).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying, . . issue fee." From the wording of 37 CFR 1.28(b), (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

16. Instructions as to Overpayment

NOTE: ". . . Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 CFR 1.26(a).

[X] Credit Account No. 04-1105.

[ ] Refund

Chris C. O'Day

Date: 1-27-04 **SIGNATURE OF PRACTITIONER**

Reg. No. 38,256

Christine C. O'Day
(type or print name of practitioner)

Tel. No.: (617) 439-4444

EDWARDS & ANGELL, LLP
P.O. Box 9169
P.O. Address

Customer No.: 21874

Boston, MA 02209

[X] **Incorporation by reference of added pages**

(check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED)

[ ] Plus Added Pages for New Application Transmittal Where Benefit of Prior U.S. Application(s) Claimed

Number of pages added _____

[ ] Plus Added Pages for Papers Referred to in Item 5 Above

Number of pages added 2

[ ] Plus added pages deleting names of inventor(s) named on prior application(s) who is/are no longer inventor(s) of the subject matter claimed in this application.

Number of pages added _____

[ ] Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added _____

[ ] **Statement Where No Further Pages Added**

(if no further pages form a part of this Transmittal, then end this Transmittal with this page and check the following item)

[X] This transmittal ends with this page.

431497

Express Mail Label No. EV 342587673 US
Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
NEW NON-PROVISIONAL PATENT APPLICATION

TITLE: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

INVENTOR: Claus MEESE and Bengt SPARF

FILING DATE: January 27, 2004

ATTORNEY: Peter F. Corless (Reg. No. 33,860)
EDWARDS & ANGELL, LLP
P. O. Box 55874
Boston, Massachusetts 02205
Tel: (617) 439-4444
Fax: (617) 439-4170

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Description

Novel derivatives of 3,3-diphenylpropylamines

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.

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

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

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

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

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared 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.

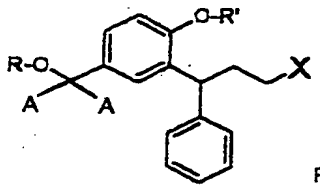
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

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

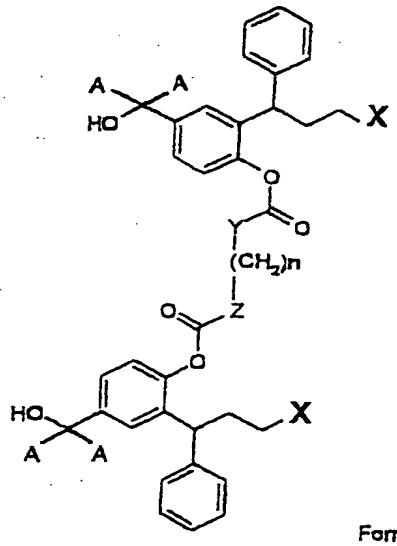
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII'



Formula I



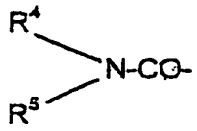
Formula VII'

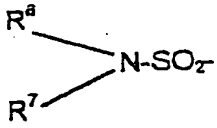
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

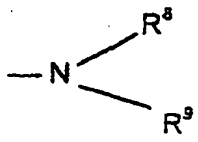
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

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

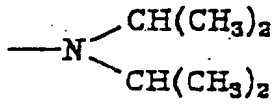
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

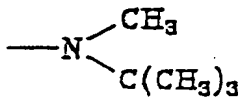
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

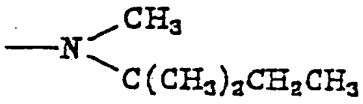
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

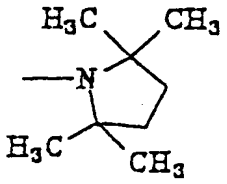
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

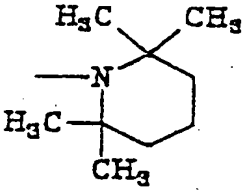
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

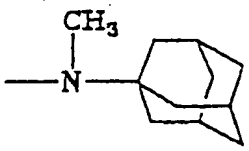
a) 

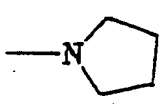
b) 

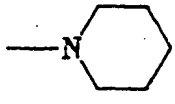
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benzyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula -CO-C_6H_5 wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. *As* substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

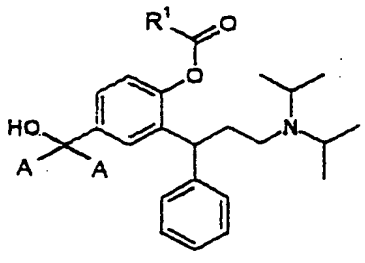
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

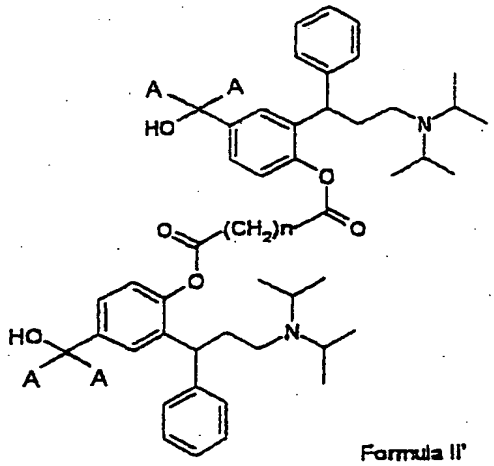
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

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



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

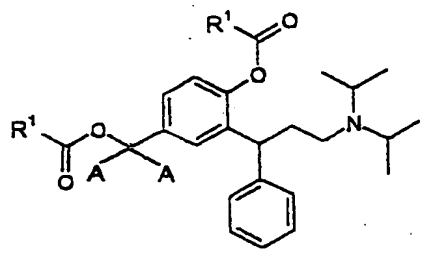
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



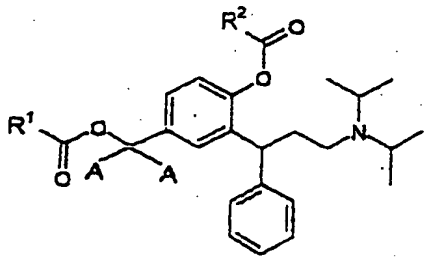
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

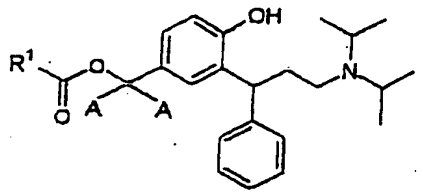
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



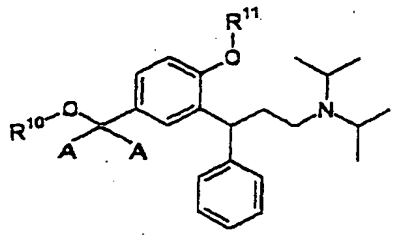
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

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



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

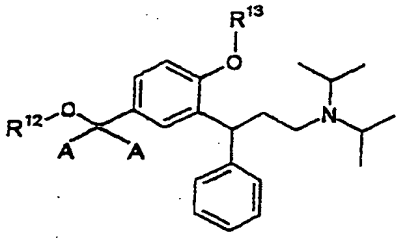
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

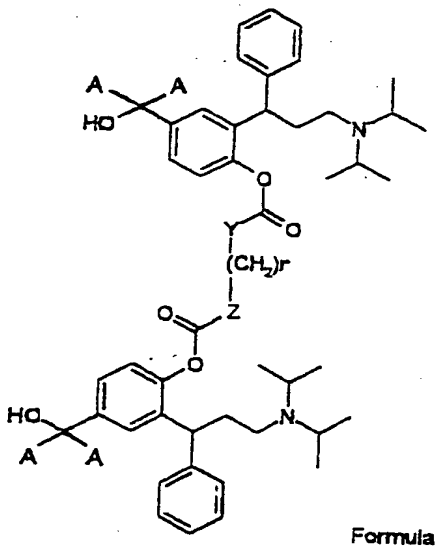
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

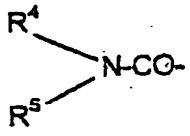


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

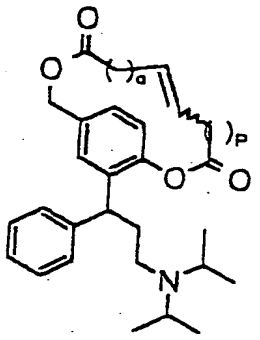
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

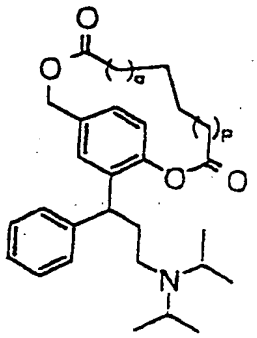
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



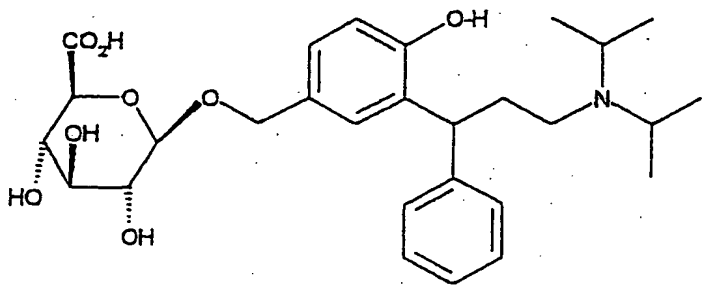
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

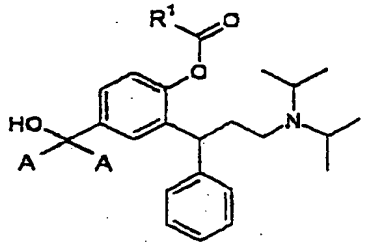


and

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.

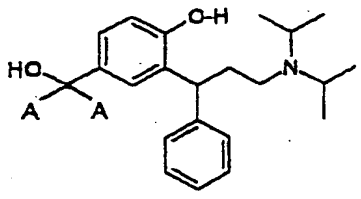
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

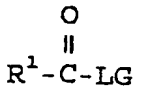


Formula II

as defined above, which comprises treatment of a compound of the formula

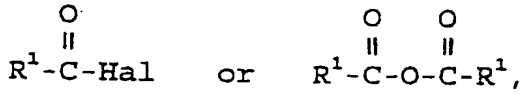


with an equivalent of an acylating agent selected from



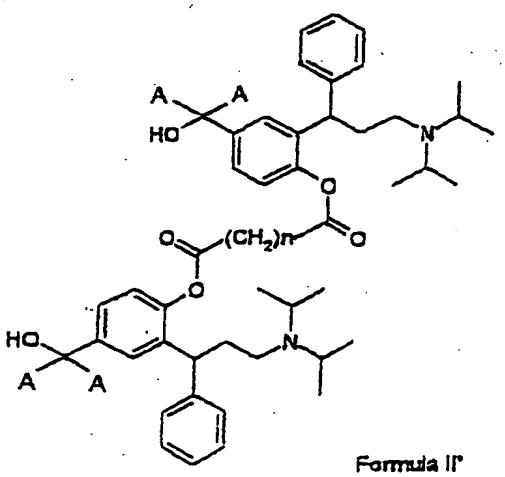
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from



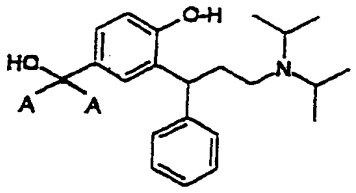
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'

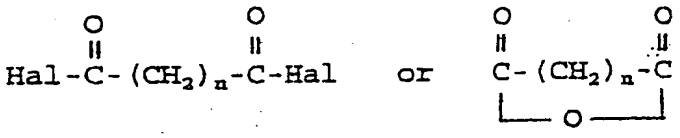


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

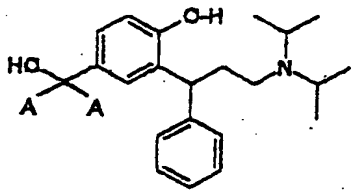


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

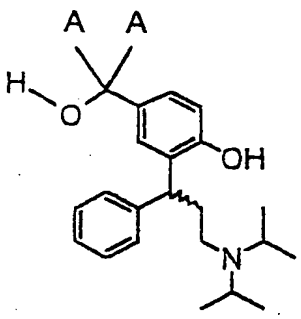
Hence, in these processes, an Intermediate B having the formula



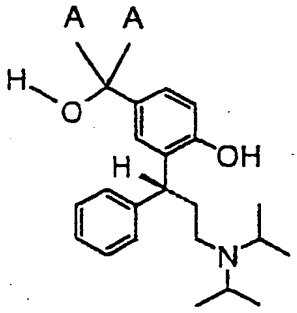
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

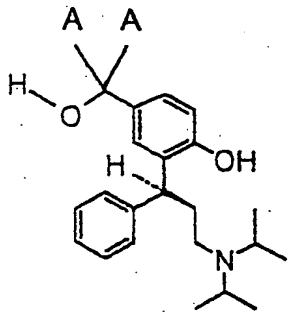
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



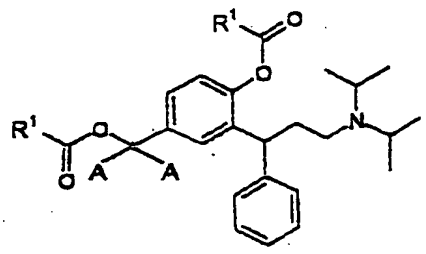
Intermediate R-(+)



Intermediate S-(-)

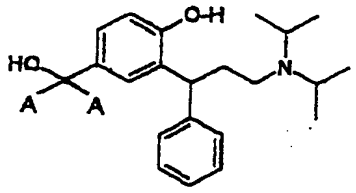
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



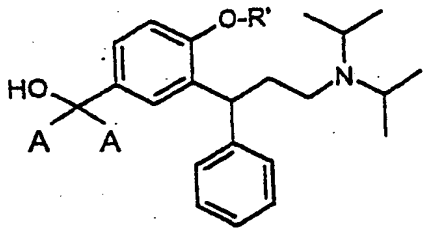
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



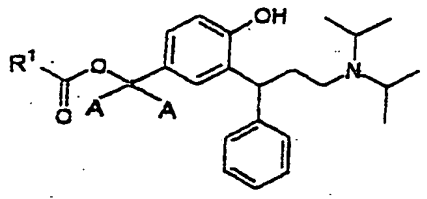
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



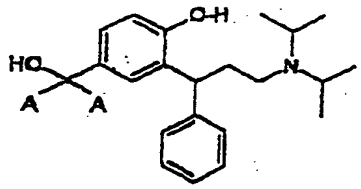
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

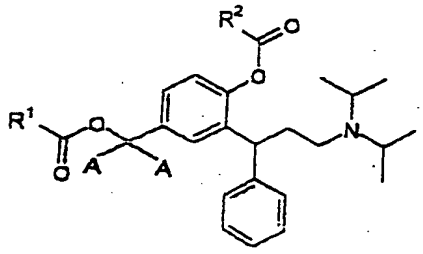


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

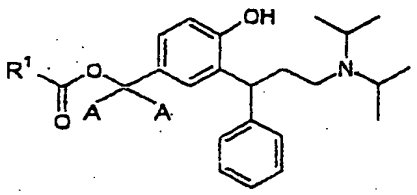
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



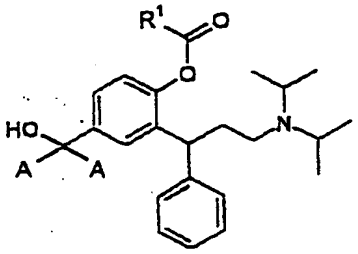
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

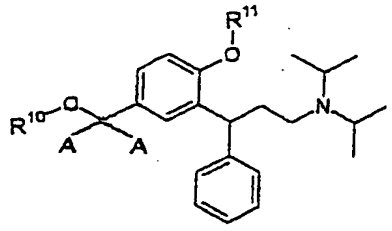


Formula II

as defined hereinbefore.

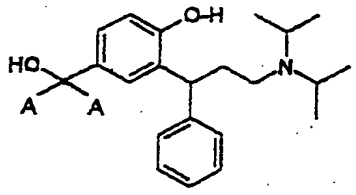
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



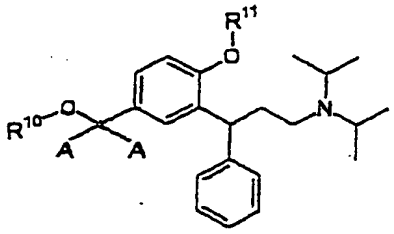
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



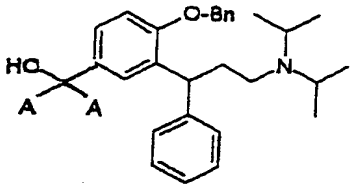
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

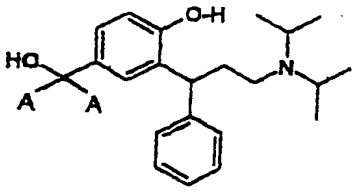


Formula VI

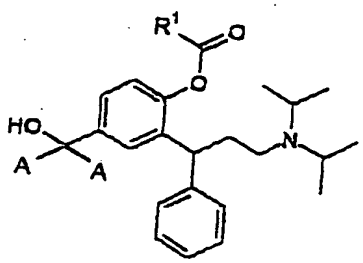
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

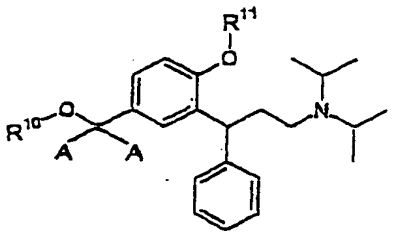


and



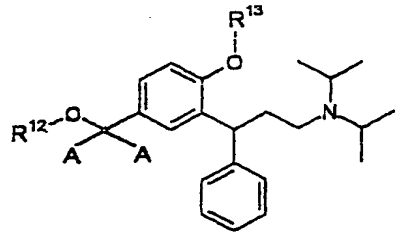
Formula II

or



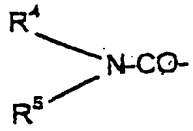
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



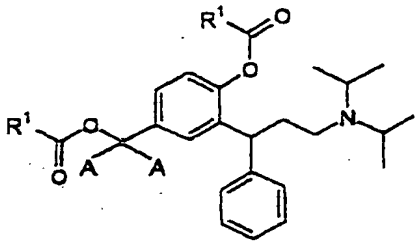
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

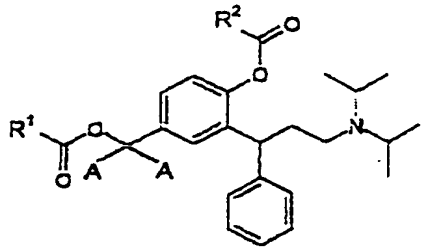


wherein R^4 and R^5 are as defined above

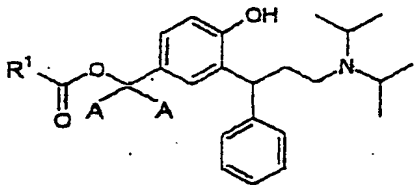
or of benzylic acylates selected from



Formula III



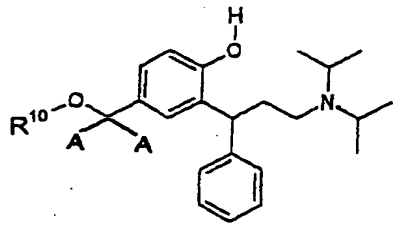
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

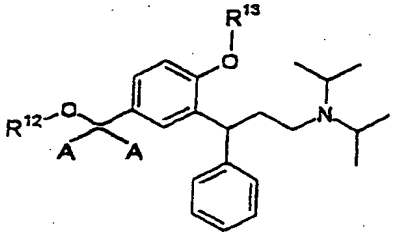


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

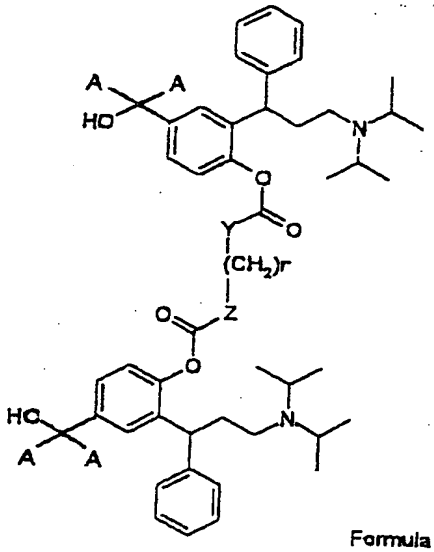
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

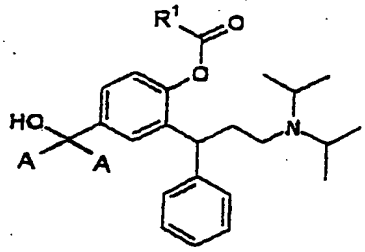


Formula VII

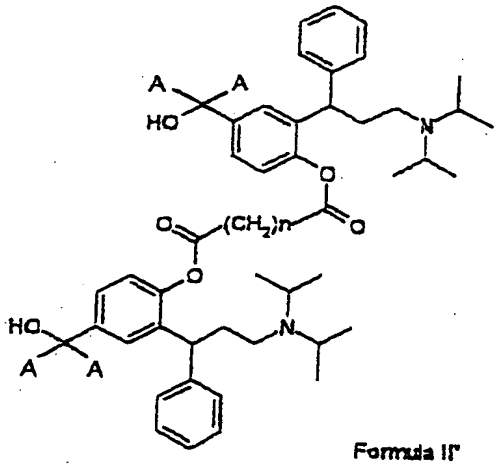


Formula VIII

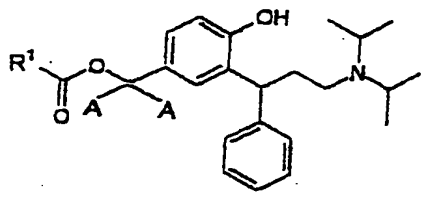
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



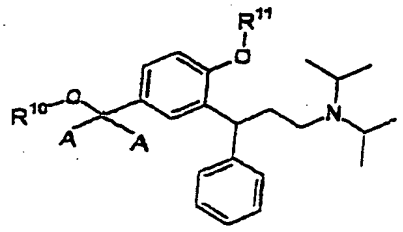
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents -C(=O)-Y-R^3, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, 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 claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, 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 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.

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.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

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

I. Experimental

1. General

All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

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

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

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

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, $M^{+\cdot}$), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

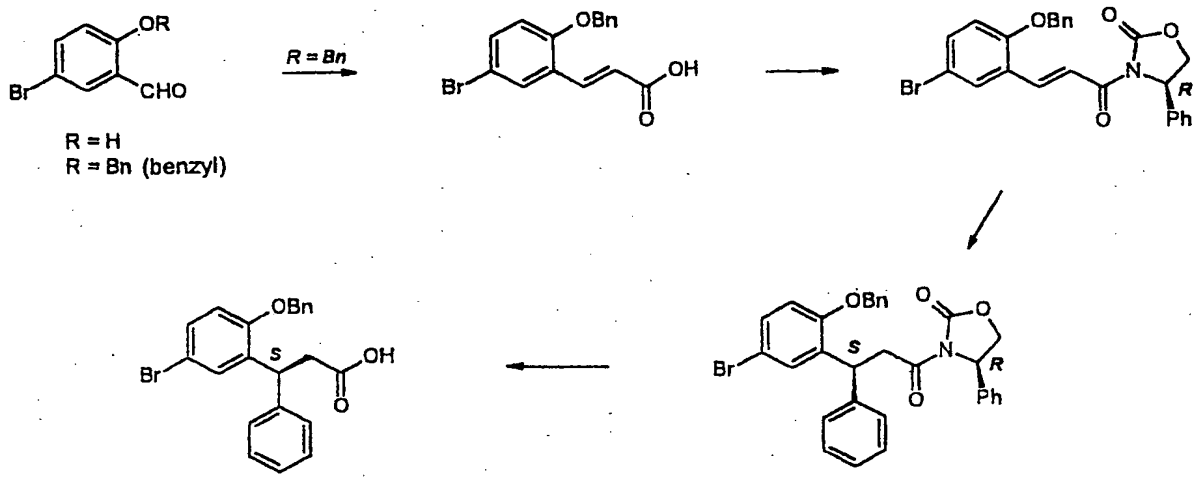
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

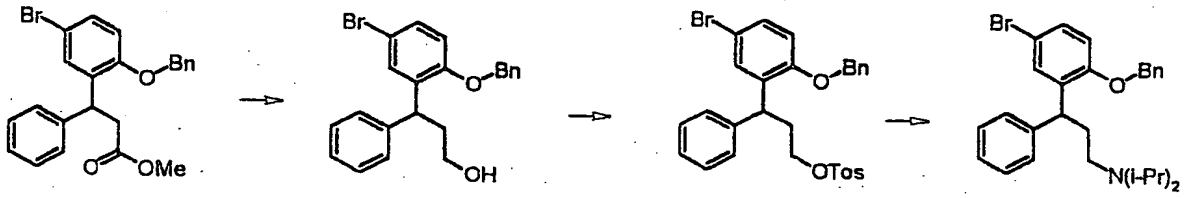
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

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

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

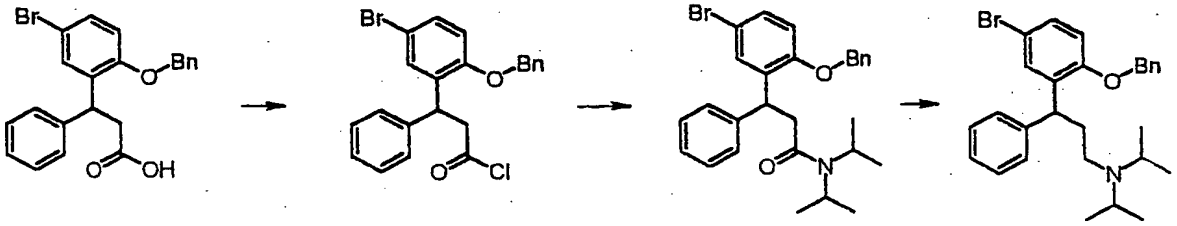
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and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

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

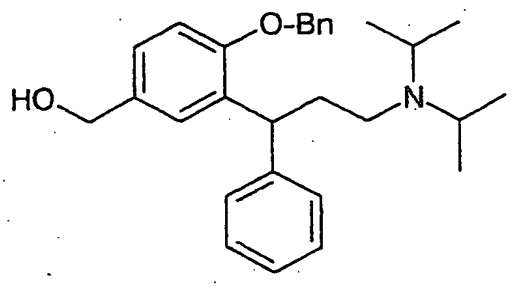
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

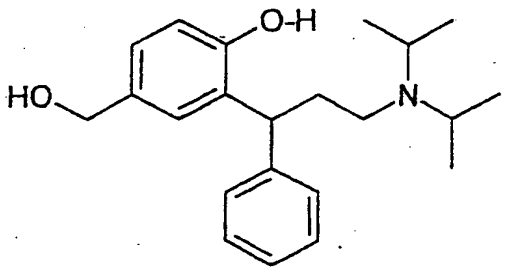
Repetition of the above described reduction of the methyl-ester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Intermediate B (n = 1)

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

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

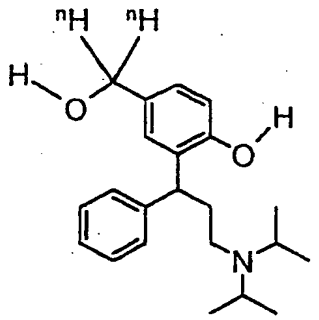
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc:(4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



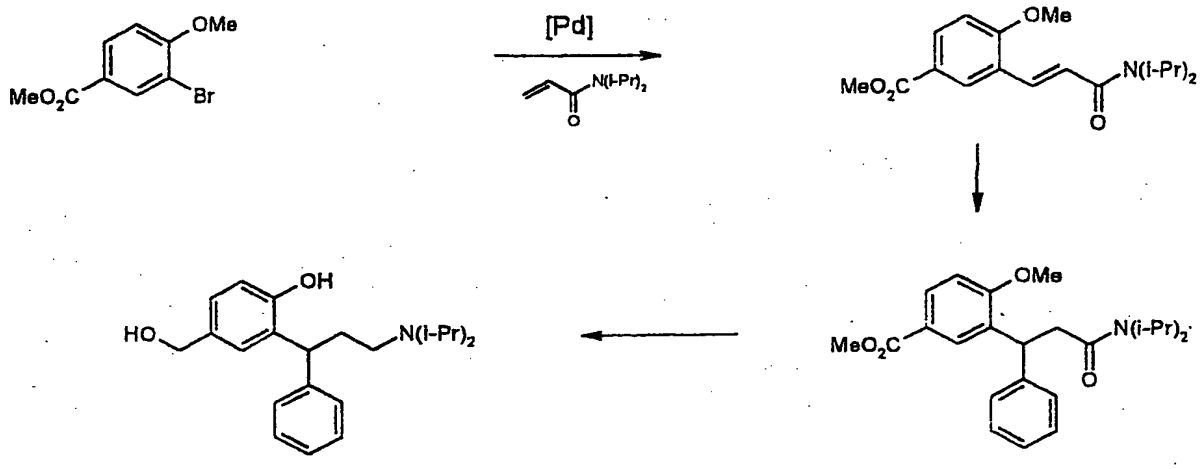
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40.

NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07.

MS (EI, DI, 105°C): 319 ($M^{+\cdot}$, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxy-benzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield).
NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of **S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate**

in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:
(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids
A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid mono-chloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

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

The following compounds were prepared according to the method described above and their analytical data are listed below:

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

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

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

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

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4); colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);
NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception 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.

Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

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

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

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

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

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

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

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed diesters

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

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

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

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

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

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

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

d) Benzylic monoesters

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

In particular, the following compounds were prepared and their analytical data are given below:

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

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

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

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

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

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

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

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

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:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m.p. 161°C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

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

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-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.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-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-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

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

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

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

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

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

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

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

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

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

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

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-di-methylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

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

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

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

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

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

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

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

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

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

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

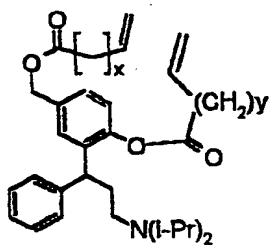
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

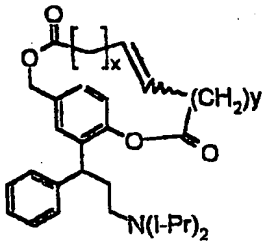
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6);
dihydrochloride m.p. 142.5-145.6°C

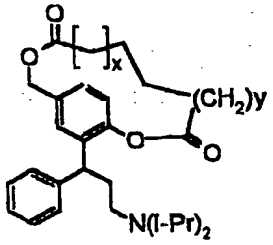
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

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

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

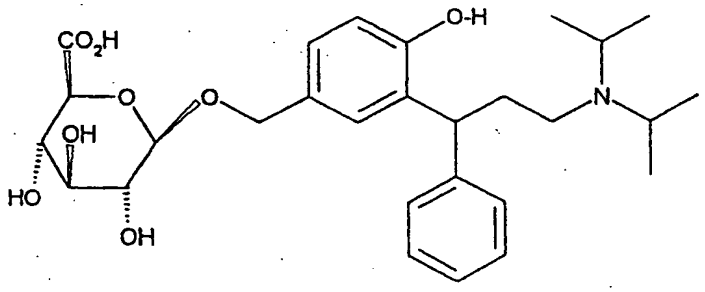
h) Inorganic ester

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester
Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol
((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

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.

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

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

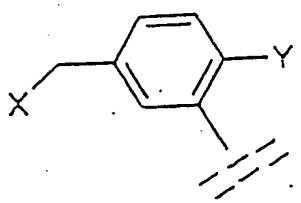
for 2 hrs at 37°C with 40 μM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

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:
The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

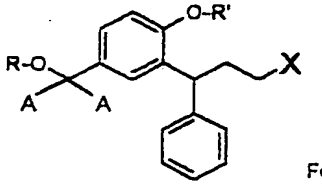
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

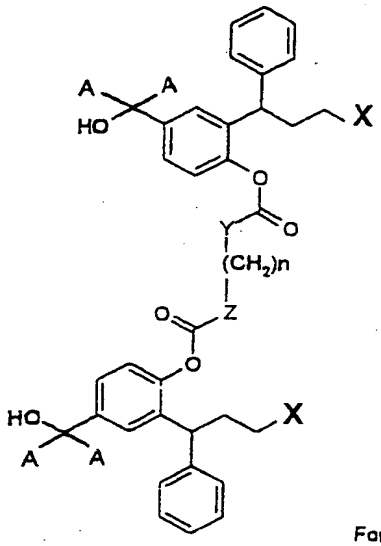
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



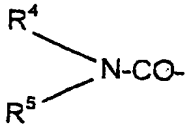
Formula VII'

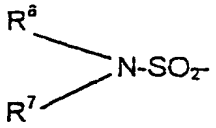
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_5 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

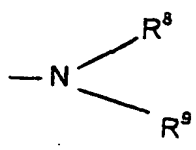
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

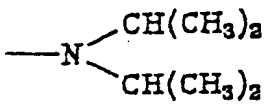
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

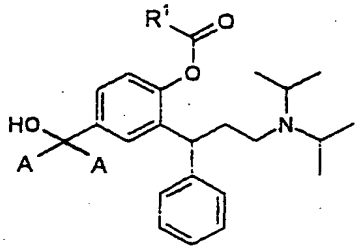
and

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

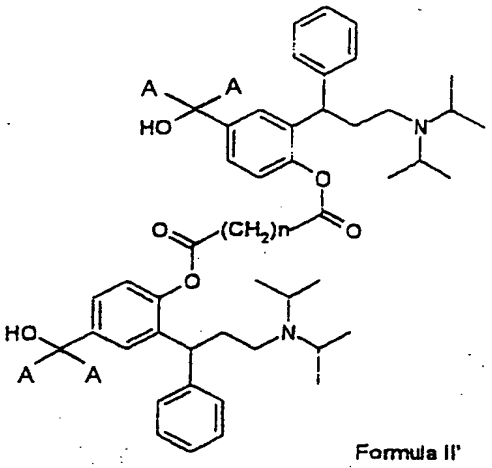
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

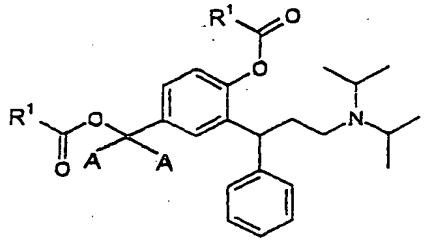
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



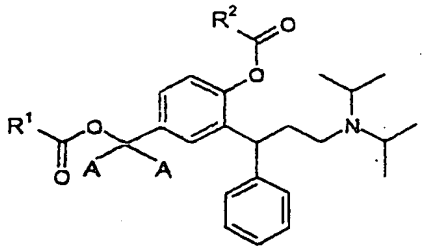
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

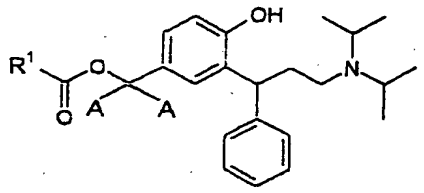
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



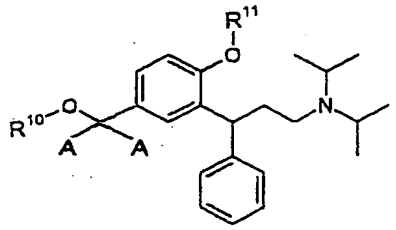
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

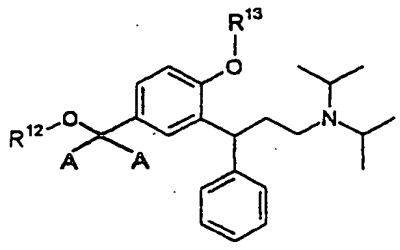
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

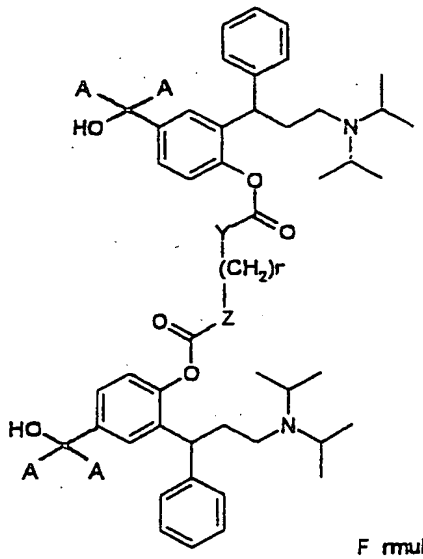
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-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-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-di-phenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropyl-amine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

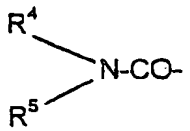


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



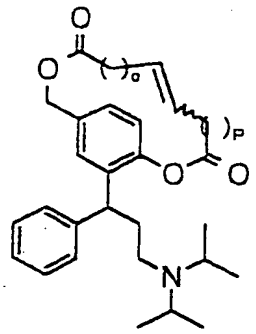
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

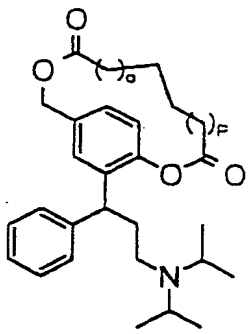
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



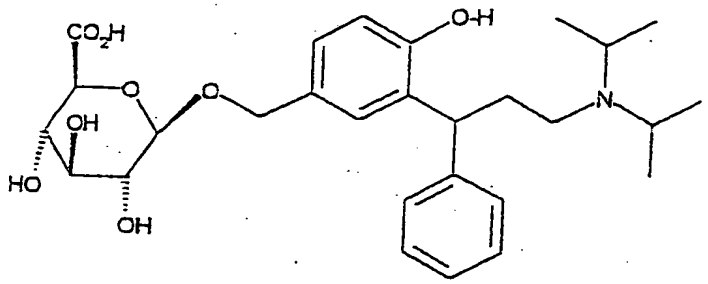
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hydroxymethyl-phenol

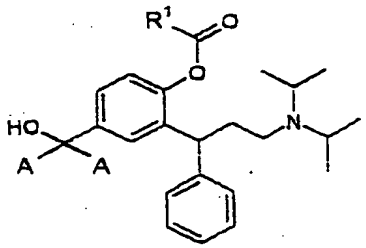
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

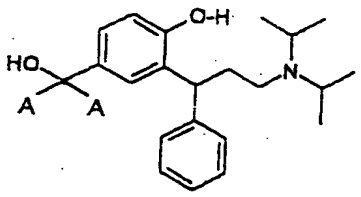
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

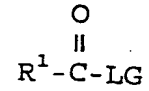


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

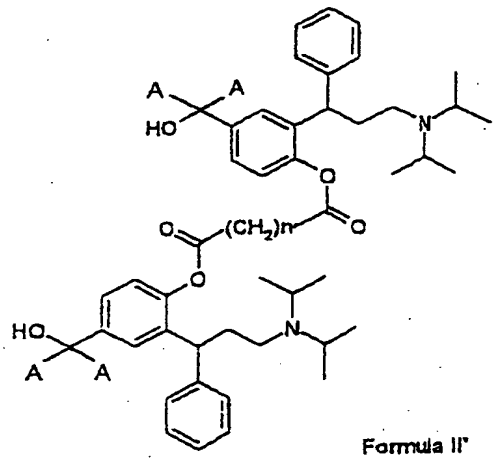


with an equivalent of an acylating agent selected from



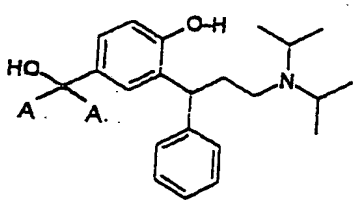
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

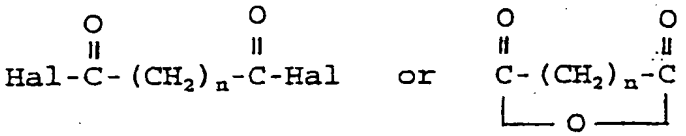


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

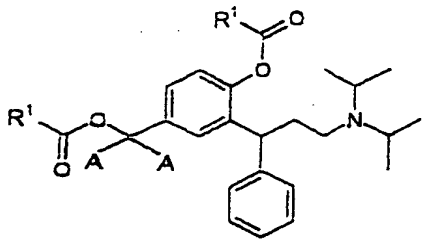


with an acylating agent selected from



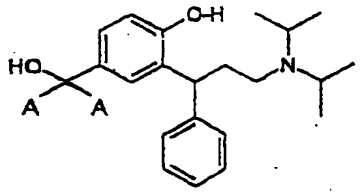
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



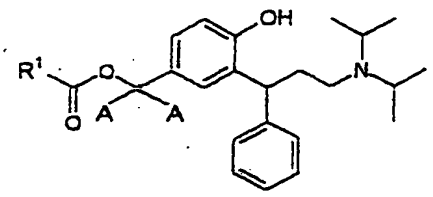
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



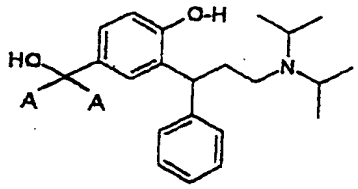
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



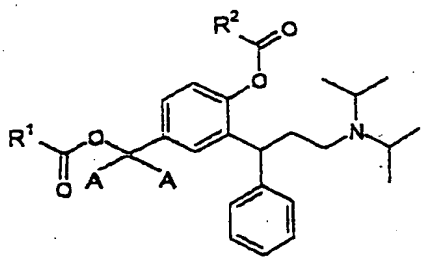
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



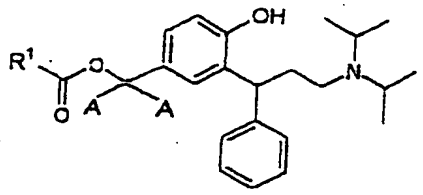
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

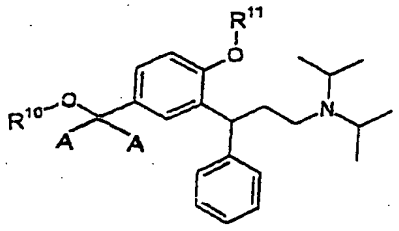
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

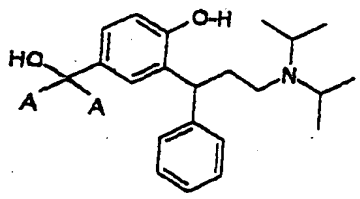
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



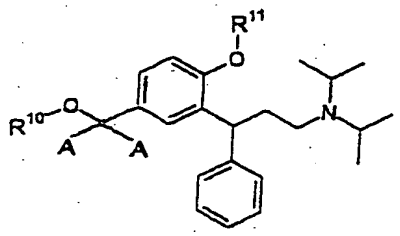
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



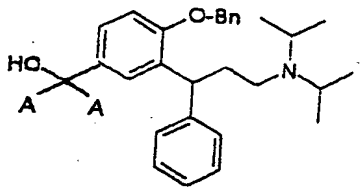
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

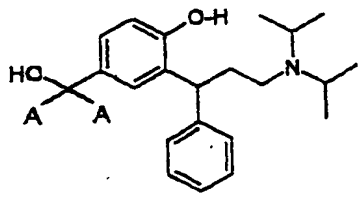


Formula VI

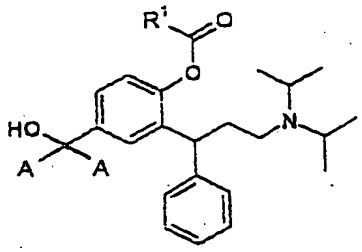
wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

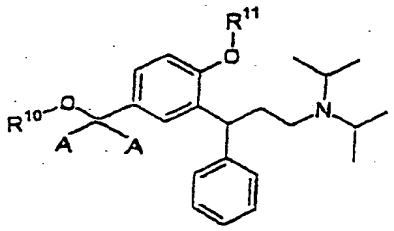


and



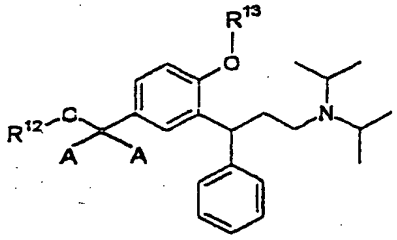
Formula II

or



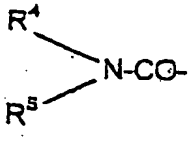
Formula VI

wherein R^{10} is hydrogen or

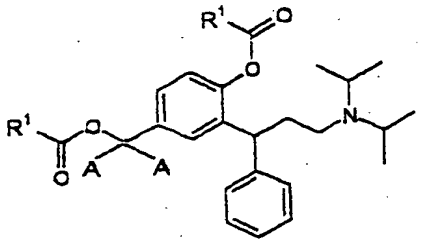


Formula VII

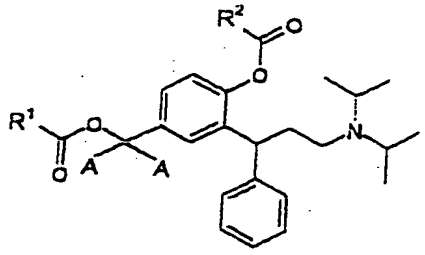
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



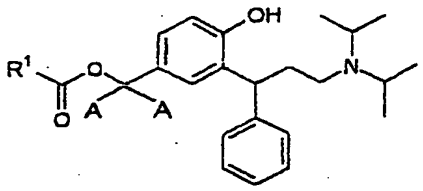
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



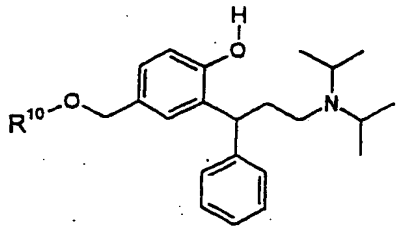
Formula IV



Formula V

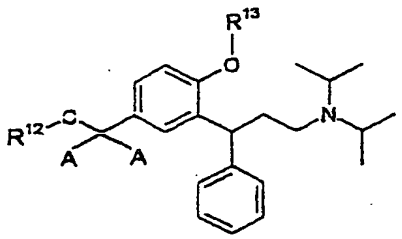
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

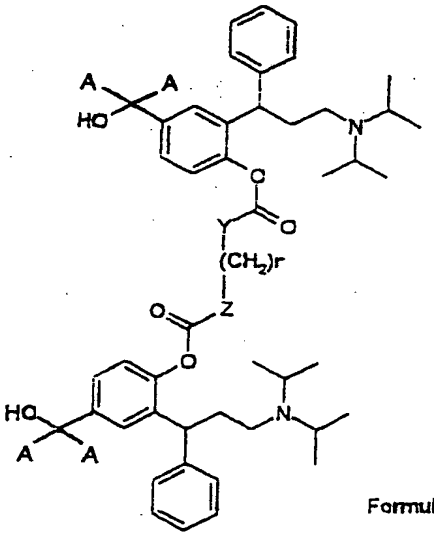


with an alkylating agent selected from alkyl halcgenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

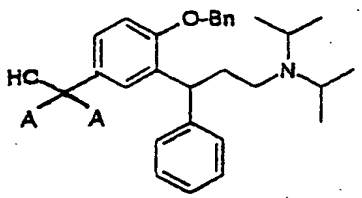


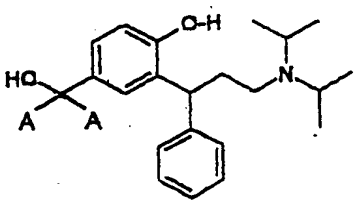
Formula VII

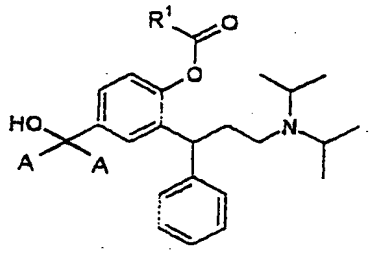


Formula VIII

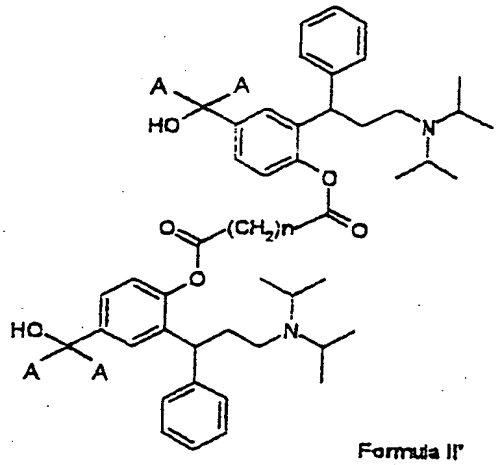
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



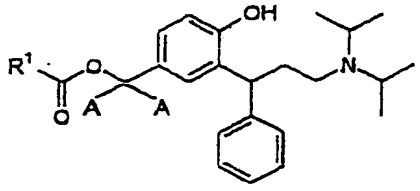




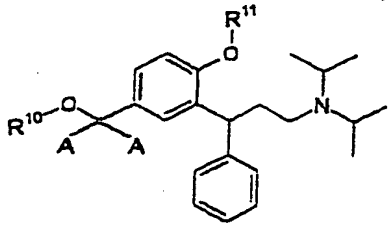
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 1/00, 217/62, 217/48, 219/28, 219/22, C07D 207/06, 295/06, C07C 271/08, C07F 7/18, C07C 307/02, A61K 31/135, 31/325, 31/40, 31/435

A1

(11) International Publication Number: **WO 99/58478**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/EP99/03212

(22) International Filing Date: 11 May 1999 (11.05.99)

(30) Priority Data:
98108608.5 12 May 1998 (12.05.98) EP

(71) Applicant *(for all designated States except US)*: SCHWARZ PHARMA AG [DE/DE]; Alfred–Nobel–Strasse 10, D–40789 Monheim (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MEESE, Claus [DE/DE]; Kreuzberger Strasse 50, D–40789 Monheim (DE). SPARF, Bengt [SE/SE]; Drottningstigen 6, S–142 65 Trångsund (SE).

(74) Agent: ALBRECHT, Thomas; Kraus & Weisert, Thomas–Wimmer–Ring 15, D–80539 Munich (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, 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, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

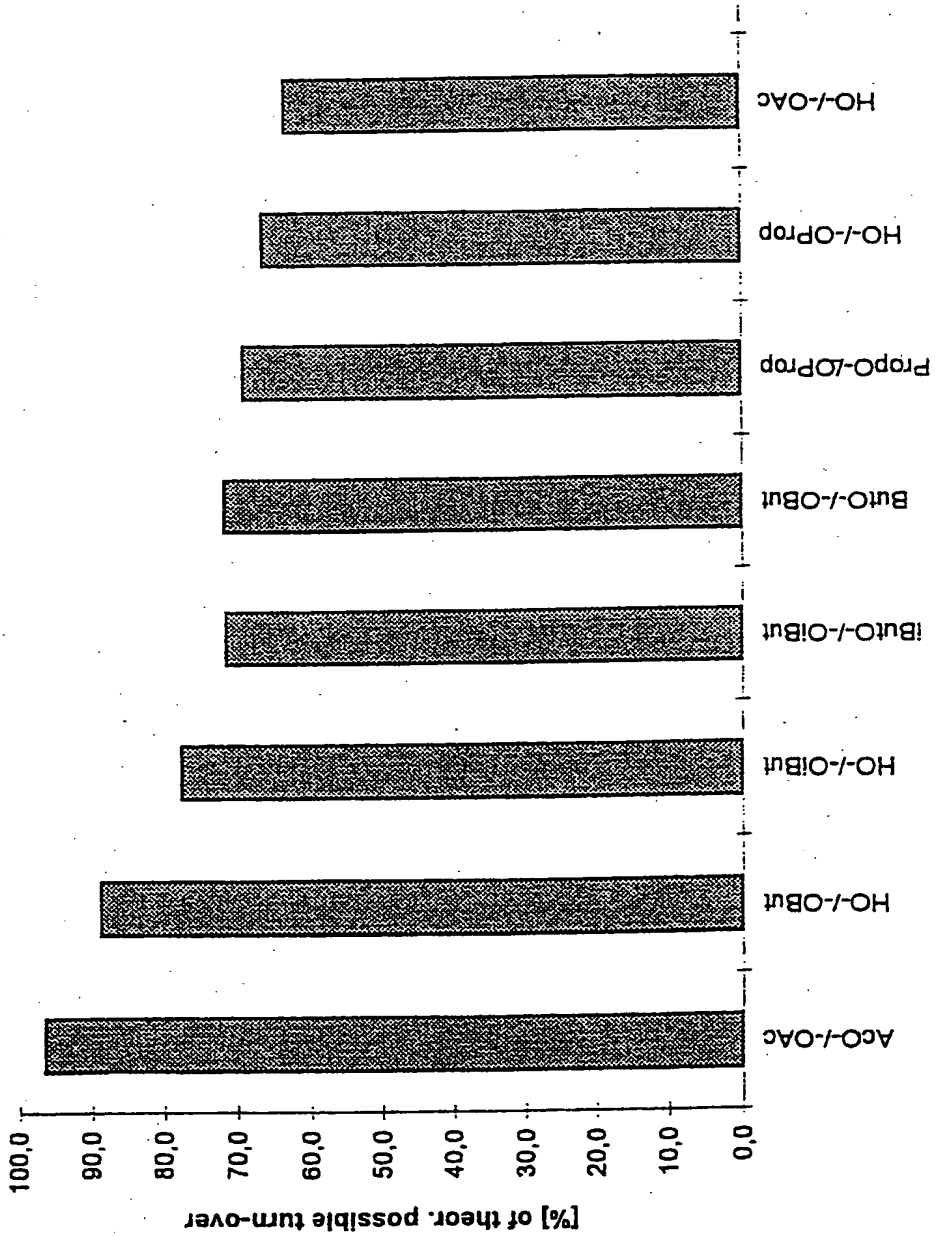
(54) Title: NOVEL DERIVATIVES OF 3,3–DIPHENYLPROPYLAMINES

(57) Abstract

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 relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

FIG. 1

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



BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Case No.: MBHB00,1121

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office 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:

Novel Derivatives of 3,3-diphenylpropylimines

the specification of which is attached hereto unless the following space is checked:

☒ was filed on November 8, 2000 as United States Application Serial Number _____

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

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

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

Prior Foreign Application(s):

	Number	Country	Day/Month/Year Filed
1.	98108608.5	EPO	12 May 1998
2.			

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

	Application Number	Filing Date
1.		
2.		

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

	Application Number	Filing Date	Status: patented, pending, abandoned
1.	PCT/EP99/03212	11 May 1999	Abandoned

LL BOEHNEN
& BERGHOFF
H WACKER DRIVE
ILLINOIS 60606
E (312) 913-0001

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and I direct that all correspondence be addressed to that Customer Number.

Customer Number: **020306**
Principal attorney or agent: Michael S. Greenfield, Reg. No. 37,142
Telephone number: 312-913-0001

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 Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Claus Meese**

Inventor's signature: Dr. Claus O. Meese Date: 8 December 2000
Residence: Germany
Citizenship: Germany
Post Office Address: Kreuzberger Strasse 50, D-40789 Monheim

Full name of second joint inventor: **Bengt Sparf**

Inventor's signature: Bengt Sparf Date: 13 December 2000
Residence: Sweden
Citizenship: Sweden
Post Office Address: Drottningstigen 6, S-142 65 Trangsund

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APRIL 02, 2001

PTAS

101591985A

MCDONNELL BOEHNEN, HULBERT & BERGHOFF
MICHAEL S. GREENFIELD
300 SOUTH WACKER DRIVE, SUITE 3200
CHICAGO, IL 60606

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/11/2001

REEL/FRAME: 011443/0478
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
MEESE, CLAUS

DOC DATE: 12/13/2000

ASSIGNOR:
SPARF, BENGT

DOC DATE: 12/13/2000

ASSIGNEE:
SCHWARZ PHARMA AG
ALFRED-NOBEL-STRASSE 10
MONHEIM, FED REP GERMANY D-40789

SERIAL NUMBER: 09700094
PATENT NUMBER:

FILING DATE: 01/02/2001
ISSUE DATE:

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

01-24-2001

101591985

FORM PTO-1595 R ET U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Attorney Ref. No.: 00,1121

To The Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying parties:

Claus Meese
Bengt Sparf

1-11-01

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Schwarz Pharma AG

Internal Address: _____

Street Address: Alfred-Nobel-Straße 10
City: Country: Zip: Monheim, Germany D-40789

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: December 13, 2000

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

09/700,094

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

RECEIVED
JAN 11 2001

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Michael S. Greenfield

Company Name: McDonnell, Boehnen, Hulbert & Berghoff

Street Address: 300 South Wacker Drive, Suite 3200

City: Chicago State: IL ZIP: 60606

6. Total number of applications ~~and patents~~ involved: 1

7. Total Fee (37 CFR 3.41).....$40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: 13-2490

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michael S. Greenfield
Printed Name of Person Signing

Signature

Date: January 9, 2001

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

01/23/2001 GTON11 00000200 09700094
FC:581 40.00 OP

FORM PTO-1595

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Attorney Ref. No.: 00,1121

To The Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying parties:

Claus Meese
Bengt Sparf

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒No

2. Name and address of receiving party(ies)

Name: Schwarz Pharma AG

Internal Address: _____

Street Address: Alfred-Nobel-Straße 10
City: Country: Zip: Monheim, Germany D-40789

Additional name(s) & address(es) attached? ☐ Yes ☒No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: December 13, 2000

4. Application number(s) or patent number(s):

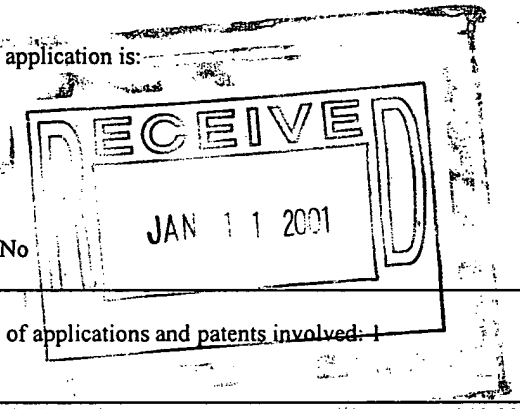
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

09/700,094

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒No



5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Michael S. Greenfield

Company Name: McDonnell, Boehnen, Hulbert & Berghoff

Street Address: 300 South Wacker Drive, Suite 3200

City: Chicago State: IL ZIP: 60606

6. Total number of applications and patents involved: 1

7. Total Fee (37 CFR 3.41).....$40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: 13-2490

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michael S. Greenfield
Printed Name of Person Signing

Signature

Date: January 9, 2001

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

ASSIGNMENT

Case No.: MBHB00, 1121
Inventors:
Date of Execution
of Application:

Serial No.:

Filing Date: November 8, 2000

In consideration of One Dollar ($1.00) and other good and valuable considerations in hand paid, the receipt and sufficiency whereof are hereby acknowledged, the undersigned hereby assign to:

Schwarz Pharma AG, at Alfred-Nobel-Straβe 10, D-40789 Monheim, Germany

its successors and assigns, the entire right, title and interest in the invention or improvements of the undersigned disclosed in an application for Letters Patent of the United States, entitled:

Novel Derivatives of 3,3-Diphenylpropylamines

and identified as:

Case No. MBHB00,1121

in the offices of McDONNELL BOEHNEN HULBERT & BERGHOFF and in said application and any and all other applications, both United States and foreign, which the undersigned may file, either solely or jointly with others, on said invention or improvements, and in any and all Letters Patent of the United States and foreign countries, which may be obtained on any of said applications, and in any reissue or extension of such patents, and further assigns to said assignee the priority right provided by the International Convention.

The undersigned hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to said assignee.

The undersigned hereby authorize and request the attorneys of record in said application to insert in this assignment the filing date and serial number of said application when officially known, and the date of execution of the application.

The undersigned warrant themselves to be the owners of the entire right, title and interest in said invention or improvements and to have the right to make this assignment, and further warrant that there are no outstanding prior assignments, licenses, or other encumbrances on the interest herein assigned.

For said considerations the undersigned hereby agree, upon the request and at the expense of said assignee, its successors and assigns, to execute any and all divisional, continuation and substitute applications for said invention or improvements, and any necessary oath, affidavit or declaration relating thereto, and any application for the reissue or extension of any Letters Patent that may be granted upon said application and any and all applications and other documents for Letters Patent in foreign countries on said invention or improvements, that said assignee, its successors or assigns may deem necessary or expedient, and for the said considerations the undersigned authorize said assignee to apply for patents for said invention or improvements in its own name in such countries where such procedure is proper and further agree, upon the request of said assignee, its successors and assigns, to cooperate to the best of the ability of the undersigned with said assignee, its successors and assigns, in any proceedings or transactions involving such applications or patents, including the preparation and execution of preliminary statements, giving and producing evidence, and performing any and all other acts necessary to obtain, maintain and enforce said Letters Patent, both United States and foreign, and vest all rights therein hereby conveyed in the assignee, its successors and assigns, whereby said Letters Patent will be

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

held and enjoyed by the said assignee, its successors and assigns, to the full end of the term for which said Letters Patent will be granted, as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment had not been made.

WITNESS my hand and seal this 8th day of December, 2000

Dr. Claus Meese

Claus Meese

State of _____

County of _____

The foregoing instrument was acknowledged before me this _____ day of _____, _____ by _____

_____

NOTARY PUBLIC

WITNESS my hand and seal this 13th day of December, 2000.

Bengt Sparf

Bengt Sparf

State of Sweden

County of Uppsala

The foregoing instrument was acknowledged before me this 13th day of December, 2000 by Bengt Sparf

Gunnar Ljungman

NOTARY PUBLIC in Uppsala Sweden

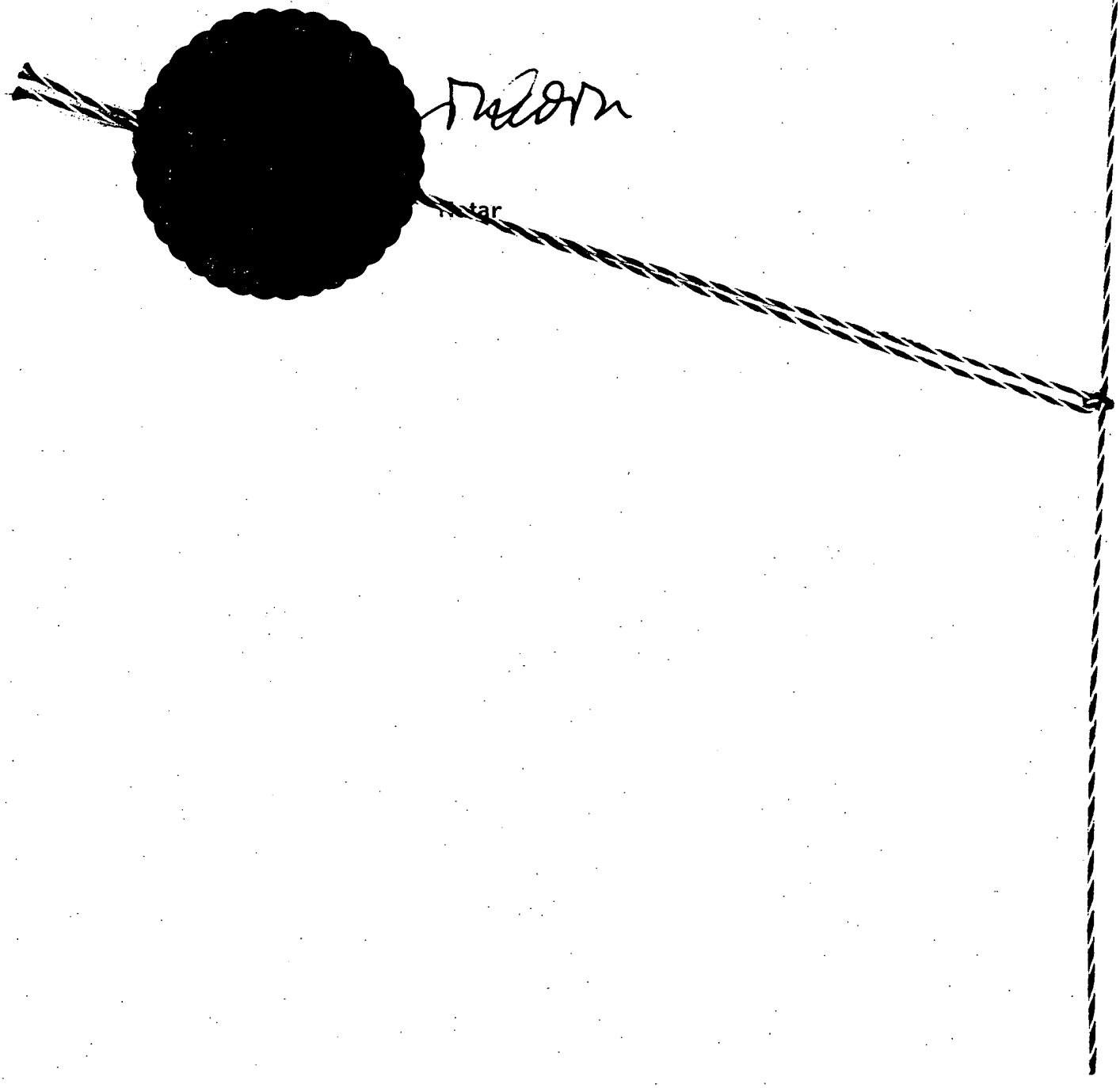
Gunnar Ljungman

Fee: SEK 180

UR. Nr. 1613 für 2000

Die umstehende Unterschrift von Herrn Dr. Claus Othmar **Meese**, geboren am 17. Juli 1945, wohnhaft Kreuzberger Straße 50 in 40789 Monheim am Rhein, ausgewiesen durch Vorlage seines Personalausweises, beglaubige ich hiermit aufgrund vor mir erfolgter Fertigung.

Monheim am Rhein, den 08. Dezember 2000



Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese, et al.

SERIAL NO.: Not Yet Assigned
[Continuation of USSN 09/700,094]
[Express Mail Label EV 342587673US]

FILED: Herewith

FOR: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Mail Stop: Patent Application
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

PRELIMINARY AMENDMENT

Applicants kindly ask that the above-identified application, filed herewith, be amended prior to examination as set forth below.

Amendments to the specification are reflected on page 2 of this paper.

Amendments to the claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks begin on page 21 of this paper.

Amendments to the specification:

On page 1, please insert the following paragraph following the title of the invention:

The present application is a Continuation Application of USSN 09/700,094, filed January 2, 2001, which in turn claimed the priority benefit of PCT/EP99/03212, filed May 11, 1999.

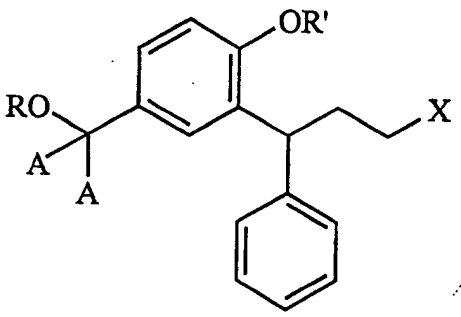
REMARKS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

Claims 1-27 (cancelled).

Claim 28 (new): A 3,3-Diphenylpropylamine of the formula I:

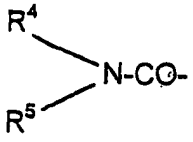


Formula I

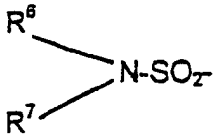
wherein R and R' are independently

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate;

b) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue;



c) wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen;



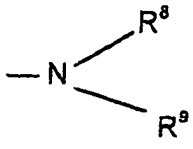
d) wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms;

e) an ester moiety of inorganic acids, or

f) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently C_1-C_4 alkyl or aryl,

with the proviso that at least one of R' and R is not hydrogen, and the proviso that R' is not methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia



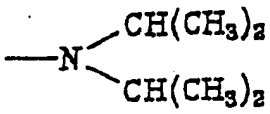
Formula Ia

wherein R^8 and R^9 represent C_1-C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

A represents hydrogen (^1H) or deuterium (^2H), and

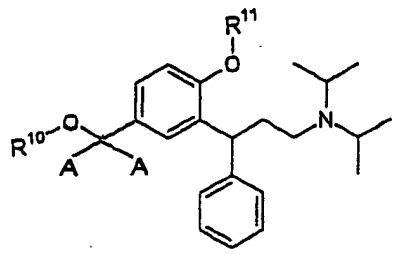
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

Claim 29 (new): The 3,3-Diphenylpropylamine as claimed in claim 28, wherein X is



Claim 30 (new): The 3,3-Diphenylpropylamine as claimed in claim 29 selected from:
(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl] ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester.

Claim 31 (new): A 3,3-Diphenylpropylamine of the formula VI:



Formula VI

wherein A represents hydrogen (^1H) or deuterium (^2H), and

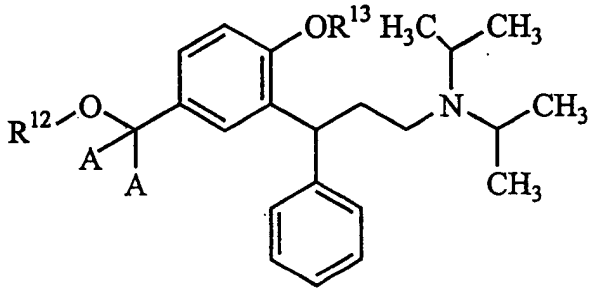
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers, and

wherein one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl, alkoxycarbonyl, $C(O)NR^4R^5$ and $-SiR_aR_bR_c$ and the other of R^{10} and R^{11} represents hydrogen.

Claim 32 (new): The 3,3-Diphenylpropylamine as claimed in claim 31 selected from the group consisting of:
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-methoxymethyl-phenol,
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-l-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,

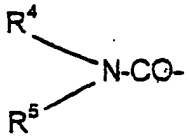
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-l-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-l-phenylpropyl)-phenyl ester,
(±)-4-(tert-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-l-phenylpropyl)-phenol,
(±)-{3-[2-(tert-butyl-diphenylsilanyloxy)-5-(tert-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-l-phenyl-propyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-l-phenylpropyl)-benzyl ester, and
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol.

Claim 33 (new): The 3,3-Diphenylpropylamines as claimed in claim 31 selected from carbonates and carbamates represented by the formula VII



Formula VII

wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



Claim 34 (new): The 3,3-Diphenylpropylamine as claimed in claim 33 selected from

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-l-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-l-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-l-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-l-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-l-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

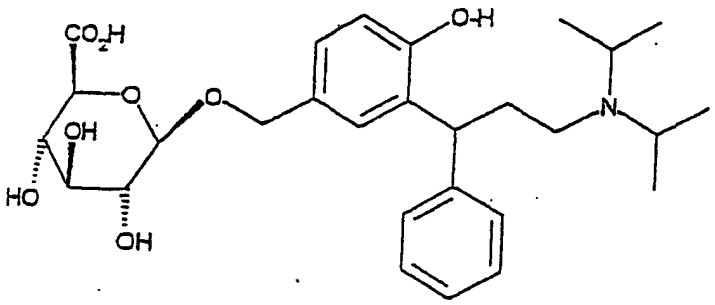
(±)-carbonic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, and

(±)-carbonic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

Claim 35 (new): The 3,3-Diphenylpropylamine selected from the group consisting of:

(i) (±)-Benzoic acid 2-(3-diisopropylamino-l-phenylpropyl)-4-sulphooxymethyl-phenyl ester,

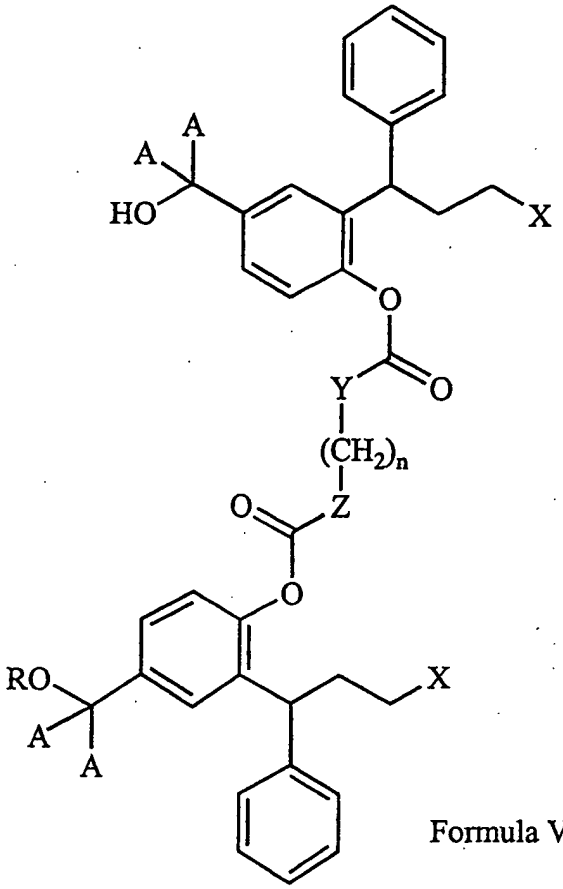
(ii) (±) -2- (3-Diisopropylamino-1-phenylpropyl) -4- (1β-D-glucuronosyloxymethyl)- phenol having the formula



and

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

Claim 36 (new): A 3,3-Diphenylpropylamine of the formula VII':



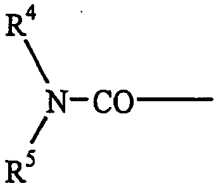
Formula VII'

wherein R is

a) C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate;

b) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue;

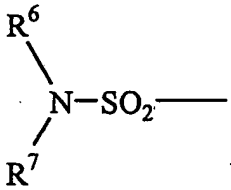
c)



wherein R^4 and R^5 independently

represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen;

d)



wherein R^6 and R^7 independently

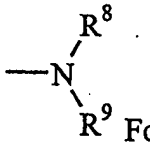
represent C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms;

e) an ester moiety of inorganic acids; or

f) $-SiR_aR_bR_C$, wherein R_a, R_b, R_c, are independently selected from C_1-C_4 alkyl or aryl,

with the proviso that R′ is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R′ is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

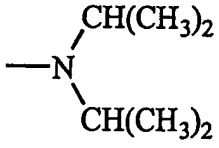
Y and Z independently represent O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

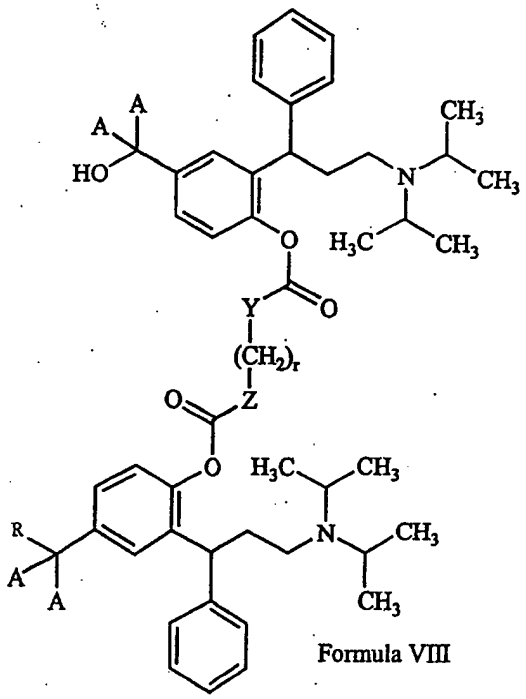
n is 0 to 12, and

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

Claim 37 (new): The 3,3-Diphenylpropylamines as claimed in claim 36, wherein X is



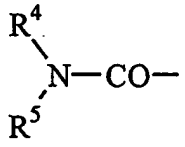
Claim 38 (new): The 3,3-Diphenylpropylamine as claimed in claim 37 selected from carbonates and carbonates represented by the formula VIII:



Formula VIII

wherein Y and Z independently represent O or NH, and

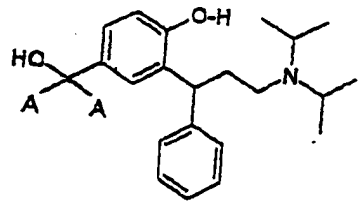
R represents a C_1-C_6 alkoxycarbonyl group or



Claim 39 (new): A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 28-38 and a pharmaceutically acceptable carrier.

Claim 40 (new): A pharmaceutical composition of claim 39 wherein the composition is a patch formulation.

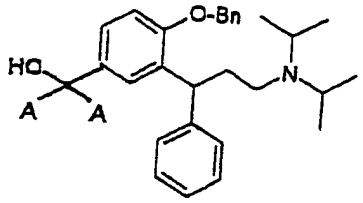
Claim 41 (new): A process for the production of ethers according to claim 31, wherein R^{11} is hydrogen, which comprises reacting a compound of the formula



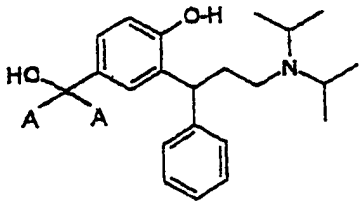
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

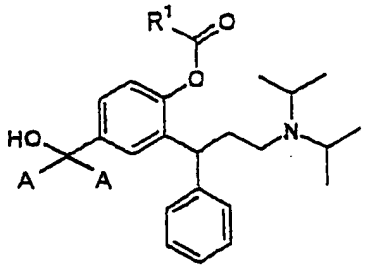
Claim 42 (new): A process for the preparation of ethers according to claim 31, which comprises acid or base treatment, in the presence of suitable hydroxy reagents, of a compound selected from

(a)

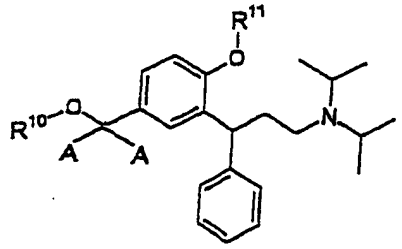


(b)



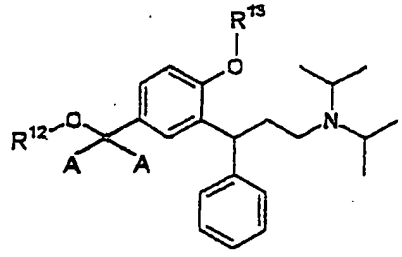


(c) Formula II



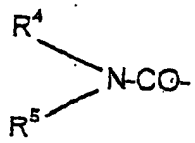
(d) Formula VI

wherein R^{10} is hydrogen,



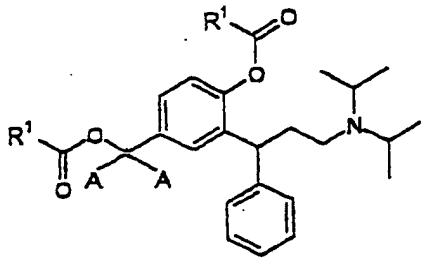
(e) Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

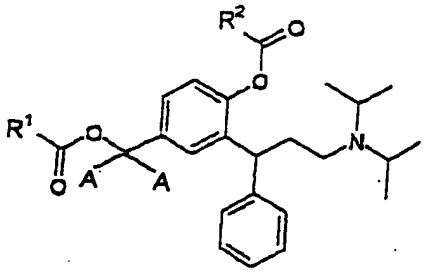


wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen, and

(f) benzylic acylates selected from

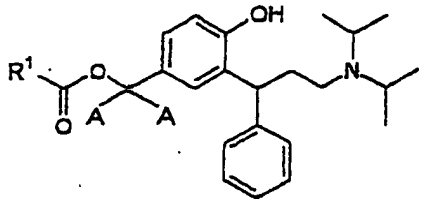


Formula III



Formula IV

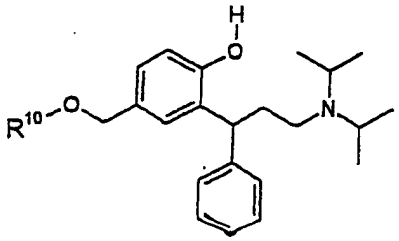
and



Formula V

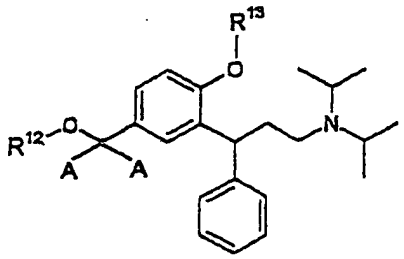
wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl, and R^2 represents hydrogen, C_1-C_6 alkyl or phenyl, with the proviso that R^1 and R^2 are not identical.

Claim 43 (new): A process for the preparation of ethers of formula VI according to claim 31, which comprises treating a compound of the formula



with an alkylating agent selected from alkyl halides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

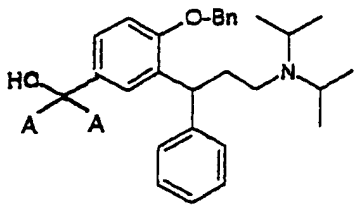
Claim 44 (new): A process for the preparation of carbonates and carbamates as claimed in claim 33, represented by formula VII:



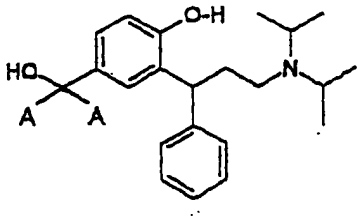
Formula VII

which comprises reacting a compound selected from the group consisting of

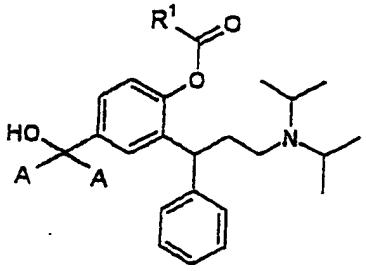
(a)



(b)

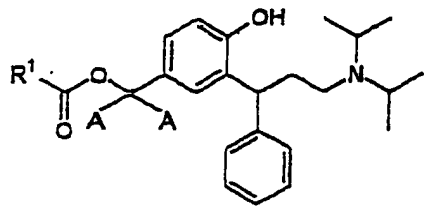


(c)



Formula II

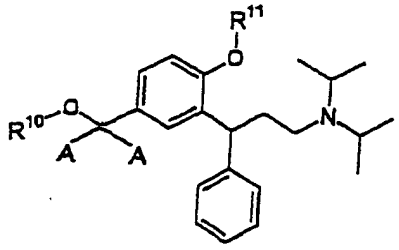
(d)



Formula V

and

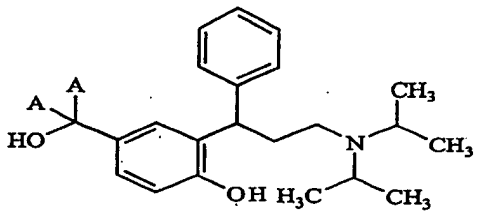
(e)



Formula VI

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is C_1-C_6 alkyl, benzyl, $-SiR_aR_bR_c$, C_1-C_6 alkylcarbonyl or benzoyl, wherein R_a, R_b, R_c are independently C_1-C_4 alkyl or aryl,
with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

Claim 45 (new): A process for the preparation of carbonates and carbamates according to claim 33 which comprises reacting a compound of formula



with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, isocyanates and isothiocyanates.

Claim 46 (new): A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 28-38.

Claim 47 (new): A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim 39 effective to diminish or eliminate symptoms of the disease.

Claim 48 (new): The method according to claim 47 wherein the disease is urinary incontinence.

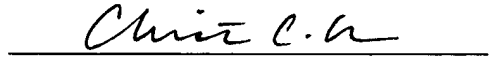
Claim 49 (new): The method according to claim 48 wherein the mammal is a human.

REMARKS

Claims 1-27 were cancelled and new claims 28-49 have been added. No new matter has been added by virtue of the amendments; support therefor being found throughout the specification and in the original claims of the application. Additionally, the within amendment is presented in large part, merely to exclude subject matter that stands allowed in parent application, USSN 09/700,094.

Early examination and allowance of the application are earnestly solicited.

Respectfully submitted,



Christine C. O'Day (Reg. 38,256)
John B. Alexander, Ph.D. (Reg. 48,399)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444

Date: January 27, 2004

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1ST AMENDMENT		AFTER 2ND AMENDMENT							
	IND	DEP	IND	DEP	IND	DEP	IND	DEP	IND	DEP	IND	DEP
1							51						
2							52						
3							53						
4							54						
5							55						
6							56						
7							57						
8							58						
9							59						
10							60						
11							61						
12							62						
13							63						
14							64						
15							65						
16							66						
17							67						
18							68						
19							69						
20							70						
21							71						
22							72						
23							73						
24							74						
25							75						
26							76						
27							77						
28	1						78						
29		1					79						
30		1					80						
31	1						81						
32		1					82						
33		1					83						
34		1					84						
35	1						85						
36	1						86						
37		1					87						
38		1					88						
39		11					89						
40		11					90						
41		1					91						
42		1					92						
43		1					93						
44		1					94						
45		1					95						
46		11					96						
47		11					97						
48		11					98						
49		11					99						
50							100						
TOTAL IND.	4						TOTAL IND.						
TOTAL DEP.	78						TOTAL DEP.						
TOTAL CLAIMS	82						TOTAL CLAIMS						

PTO-1360 (Replication only) (3-03)

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10766263

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	22	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	82 minus 20=	* 62
INDEPENDENT CLAIMS	4 minus 3 =	* 1
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	385.00	OR	BASIC FEE	770.00
XS 9=		OR	XS18=	1116.00
X43=		OR	X86=	86.00
+145=		OR	+290=	290.00
TOTAL		OR	TOTAL	2262

CLAIMS AS AMENDED - PART II

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

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
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. _____

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

02/02/2004 WABRHAM1 00000073 10766263

01 FC:1001	770.00	OP
02 FC:1202	1116.00	OP
03 FC:1201	86.00	OP
04 FC:1203	290.00	OP

Repln. Ref: 02/02/2004 WABRHAM1 0014285200
DA#:041105 Name/Number:10766263
FC: 9204 $212.00 CR

PTO-1556
(5/87)

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

Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: C. Meese et al.

Serial No.: 10/766,263 GROUP: Not Yet Assigned

Filed: January 27, 2004 EXAMINER: Not Yet Assigned

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

****

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date 4/8/04 By: Susan M Dillon
Susan M. Dillon

****

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§1.56 and 1.97, Applicants herewith submit the publications and/or patents shown on the attached form PTO-1449, for consideration by the Examiner in connection with the examination of the above-identified patent application.

REMARKS

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed:

X (1) within three (3) months of the Filing Date or **before the mailing date of the First Office Action** on the merits; or

____ (2) within three months of the mailing date of the Written Opposition issued by the: _____Patent Office (dated _____); or

___ (3) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite Certification or fee under Rule 1.17(p), namely $180.00, is included herein; or

___ (4) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

It is respectfully requested that each of the documents shown on the attached form(s) PTO-1449 be made of record in this application. Copies of these documents (CHECK ONE):

_X_ Patent No. 5,686,464 is enclosed herewith; and

_X_ all others have been cited in the parent application, and are thus not being resubmitted herein.

Early examination and allowance of the present application are respectfully solicited.

FEE AUTHORIZATION

Should any fees associated with the submission be required, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 04-1105. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,

Christine C. O'Day (Reg. 38,256)
Edwards & Angell, LLP
PO Box 55874
Boston, MA 02205
(617) 439-4444

Date: 4-9-04

FORM PTO-1449	DOCKET NO.: 55647-C (45107)	SERIAL NO.: 10/766,263
INFORMATION DISCLOSURE STATEMENT	APPLICANT(S): C. Meese et al.	
	FILING DATE: January 27, 2004	GROUP NO.: Not Yet Assigned

UNITED STATES PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	6,313,132 B1	11/6/01	R. Johansson, et al.	514	277	
	AB	5,686,464	11/11/97	R. Johansson et al.	514	315	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES/NO
	AC	WO 89/06644	7/27/89	WIPO			
	AD	WO 94/11337	5/26/94	WIPO			

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

	AD	Nilvebrant et al., *European Journal of Pharmacology*, 327(1997) pp. 195-207.
	AE	Nilvebrant et al., *Pharmacology and Toxicology*, Vol. 81, pp. 169-172, 1997
	AF	Nilvebrant et al., *Life Sciences*. Vol. 60 (13/14), pp. 1129-1136, 1997
	AG	Postlind et al., *Drug Metabolism and Disposition*, Vol. 26 (4), pp. 289-293, 1998
	AH	Andersson et al., *Drug Metabolism and Disposition*, Vol. 26 (6), pp. 528-535, 1998
	AI	Brynne et al., *J. Clin. Pharm. Ther.*, Vol. 35 (7), pp. 287-295, 1997

Examiner:	Date:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	55647-C (45107)	3433

21874 7590 09/28/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *18-49* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/700,094.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12Apr04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 28, 29, 31, 32, 36, 37, 39, 41-43 and 46-49 (all in part), drawn to compounds of formulae (I), (VII) and (VII'), wherein both of or one of R and R' is alkyl, cycloalkyl or benzyl, the other one of R and R' being hydrogen when both are not as defined as in this Group, classified in class/subclass 564/316 (aromatic amines with an ether function), a process for making the compounds, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

II. Claims 28, 29, 31, 33, 34, 36-39 and 44-49 (all in part), drawn to carbonate compounds of formulae (I), (VI), (VII), (VII') and (VIII) wherein both of or one of R and R' is alkoxycarbonyl, aryloxycarbonyl or benzoylcarbonyl, the other one of R and R' being hydrogen when both are not as defined as in this Group, classified in class/subclass 558/269 (compounds with two carbonate groups), 558/275 (when only R is a carbonate group), 558/276 (when only R' is a carbonate group), a process for making the compounds, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

III. Claims 28, 29, 32, 35, 36, 37, 39, 46, 47 and 49 (all in part) drawn to compounds of formulae (I) and (VII), wherein both of R and R' or one of R and R' are a carbohydrate, classified in class 536 (different subclasses

depending on the identity of the carbohydrate moiety), pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

IV. Claims 28, 29, 30, 35, 36, 37, 38, 39 and 46-49 (all in part) drawn to compounds of formulae (I), (VII) and (VII') wherein both of R and R' or one of R and R' are benzoylglycyl or a substituted amino acid residue, classified in class/subclasses depending on the identity of the amino acid residue, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

V. Claims 28, 29, 33, 34, 36, 37, 39 and 44-49 (all in part), drawn to compounds of formulae (I), (VI), (VII), (VII') and (VIII), wherein both of R and R' or one of R and R' are $C(O)NR^4R^5$ (carbamate esters) classified in class/subclasses 560/32 (when R^4 or R^5 is aryl) and in 560/132 (when both of R^4 and R^5 are acyclic), process for making the compounds, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

VI. Claims 28, 29, 36, 37, 39 and 46-49 (all in part), drawn to compounds of formulae (I) and (VII'), wherein both of R and R' or one of R and R' are $S(O)_2NR^6R^7$ (sulfamate esters) classified in class/subclass 558/48, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

VII. Claims 28, 29, 35, 36, 37, 39, 46-49 (all in part) drawn to compounds of formulae (I) and (VII') wherein both of R and R' or one of R and R' are esters of inorganic acids, classified according to the identity of the esterifying inorganic acid, for example, class/subclass 558/207 (phosphate esters), 558/286 (borate esters), 558/20 (sulfate esters) pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

VIII. Claims 28, 29, 31, 32, 36, 37, 39, 31 and 46-49 (all in part) drawn to compounds of formulae (I), (VI) and (VII') wherein both of R and R' or one of R and R' are a silanyl group $-SiR_aR_bR_c$, classified in class/subclass 556/465, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

IX. Claims 28, 29, 32, 33, 34, 36, 37, 38, 39 and 46-49 (all in part) drawn to compounds according to formulae (I), (VII) and (VII') wherein one of R and R' is a different functional group from Groups I-VIII hereinabove than the other one of R and R' – mixed compounds. These compounds are variously classified, according to the combination of functional groups. Further restriction could be required if this group is elected.

X. Claim 30 (in part), the second through fifth compounds named in the claim, classified in class 560. These compounds have been patented in US 6,713,464, the parent case of the instant application.

XI. Claim 40, drawn to a drug delivery device for administering a compound of formulae (I), (VI), (VII), (VII') and (VIII), (a patch), classified in class/subclass 424/449. Further restriction will be required should this Group be elected.

The inventions are distinct, each from the other because:

As evidenced by the different classifications, the compounds set forth in Groups I-X above have acquired a separate status in the art and would require separate searches which are not overlapping. Each one of the Groups set forth in this requirement is not an obvious variant of any other Group herein. So, each group requires a different search of the chemical literature to evaluate the patentability of compounds in that Group.

The compounds falling into the different categories I-X set forth above are patentably distinct as well.

Devices as set forth in Group XI require a separate search of the medical literature than do simple pharmaceutical compositions comprising the compounds. A patch is actually not a composition, it is a device.

The mixed compounds in Group IX will necessitate a search of the chemical literature relating to synthesis of such complexly substituted compounds in order to evaluate compliance with the first paragraph of 35 U.S.C. 112 of claims drawn to such compounds.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject

matter, restriction for examination purposes as indicated is proper. A showing of separate classification is *prima facie* evidence of:

1. Separate classification.
2. Separate status in the art.
3. Different field of search.

Comments

The second through fifth compounds named in instant claim 30, in Group IX above, have already been patented in US 6,713,464, which is the parent of the instant application.

Compounds possessing both ester and ether functions or ester and silylether functions, which are recited in claim 32, do not find antecedent basis in claim 31.

The last named compound in claim 32 also does not find antecedent basis in claim 31.

Claim 38 includes a spelling error, "...carbonates and carbonates..."

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday-Friday from 6:30am to 3:00pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-2717.

zt

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

FORM PTO-1449	DOCKET NO.: 55647-C (45107)	SERIAL NO.: 10/766,263
INFORMATION DISCLOSURE STATEMENT	APPLICANT(S): C. Meese et al.	
	FILING DATE: January 27, 2004	GROUP NO.: ~~Not Yet Assigned~~ 1624

UNITED STATES PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
ZT	AA	6,313,132 B1	11/6/01	R. Johansson, et al.	514	277	
ZT	AB	5,686,464	11/11/97	R. Johansson et al.	514	315	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES/NO
ZT	AC	WO 89/06644	7/27/89	WIPO	—	—	
ZT	AD	WO 94/11337	5/26/94	WIPO	—	—	

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

ZT	AD	Nilvebrant et al., *European Journal of Pharmacology*, 327(1997) pp. 195-207.
ZT	AE	Nilvebrant et al., *Pharmacology and Toxicology*, Vol. 81, pp. 169-172, 1997
ZT	AF	Nilvebrant et al., *Life Sciences*. Vol. 60 (13/14), pp. 1129-1136, 1997
ZT	AG	Postlind et al., *Drug Metabolism and Disposition*, Vol. 26 (4), pp. 289-293, 1998
ZT	AH	Andersson et al., *Drug Metabolism and Disposition*, Vol. 26 (6), pp. 528-535, 1998
ZT	AI	Brynne et al., *J. Clin. Pharm. Ther.*, Vol. 35 (7), pp. 287-295, 1997

Examiner: [signature] Date: 27 SEPTEMBER 2004

Index of Claims

Application No.	Applicant(s)	
10/766,263	MEESE ET AL.	
Examiner	**Art Unit**	
Zachary C. Tucker	1624	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	4/2004
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	
	14	
	15	
	16	
	17	
	18	
	19	
	20	
	21	
	22	
	23	
	24	
	25	
	26	
	27	
	28	
	29	
	30	
	31	
	32	
	33	
	34	
	35	
	36	
	37	
	38	
	39	
	40	
	41	
	42	
	43	
	44	
	45	
	46	
	47	
	48	
	49	
	50	

Claim		Date
Final	Original	
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

Claim		Date
Final	Original	
	101	
	102	
	103	
	104	
	105	
	106	
	107	
	108	
	109	
	110	
	111	
	112	
	113	
	114	
	115	
	116	
	117	
	118	
	119	
	120	
	121	
	122	
	123	
	124	
	125	
	126	
	127	
	128	
	129	
	130	
	131	
	132	
	133	
	134	
	135	
	136	
	137	
	138	
	139	
	140	
	141	
	142	
	143	
	144	
	145	
	146	
	147	
	148	
	149	
	150	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 34

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKE NO.
10/766,263	01/27/2004 RULE	514	1624	55647-C (45107)

APPLICANTS

Claus Meese, Monheim, GERMANY;

Bengt Sparf, Trangsund, SWEDEN;

** CONTINUING DATA **********

This application is a CON of 09/700,094 01/02/2001 PAT 6,713,464
which is a 371 of PCT/EP99/03212 05/11/1999

** FOREIGN APPLICATIONS **********

EUROPEAN PATENT OFFICE (EPO) 98108608.5 05/12/1998

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 06/16/2004

Foreign Priority claimed ☒ yes ☐ no 35 USC 119 (a-d) conditions met ☒ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials	STATE OR COUNTRY GERMANY	SHEETS DRAWING 1	TOTAL CLAIMS 22	INDEPENDE CLAIMS 4

ADDRESS
21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON , MA
02205

TITLE
Novel derivatives of 3,3-diphenylpropylamines

FILING FEE	FEES: Authority has been given in Paper
RECEIVED 2262	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

☐ All Fees
☐ 1.16 Fees (Filing)
☐ 1.17 Fees (Processing Ext. of time
☐ 1.18 Fees (Issue)
☐ Other _____

h e e e e e c

10-29-04 dfw

Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: C. Meese, et al.

Serial No.: 10/766,233 Group: 1624

Filed: January 27, 2004 Examiner: Z. Tucker

FOR: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date **October 27, 2004**, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number **EV517914068US**, addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, Mail Stop .Amendment

Lee Dunkle
(type or print name of person mailing paper

Lee Dunkle
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R 1.10(b).*

*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

Sir:

RESPONSE TO RESTRICTION REQUIREMENT

Applicants submit herewith the following response to the Office Communication dated September 28, 2004.

In response to the Restriction Requirement set forth in the Office Communication, Applicants elect without traverse Group I, as defined in the Office Communication to include the

subject matter of claims 28, 29, 31, 32, 36, 37, 39, 41-43 and 46-49 (all in part), drawn to compounds of formulae (I), (VII) and (VII'), wherein both of or one of R and R' is alkyl, cycolalkyl or benzyl, the other one of R and R' being hydrogen when both are not as defined as in this Group, classified in class/subclass 564/316 (aromatic amines with an ether function), a process for making the compounds, pharmaceutical compositions comprising the compounds and methods of treatment with the compounds.

The election of Group I is being made solely to comply with the Restriction Requirement set forth in the Office Communication. The right to file one or more divisional applications on non-elected subject matter is reserved.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,

Christine C. O'Day (Reg. 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444

Date: October 27, 2004

Connecting via Winsock to STN

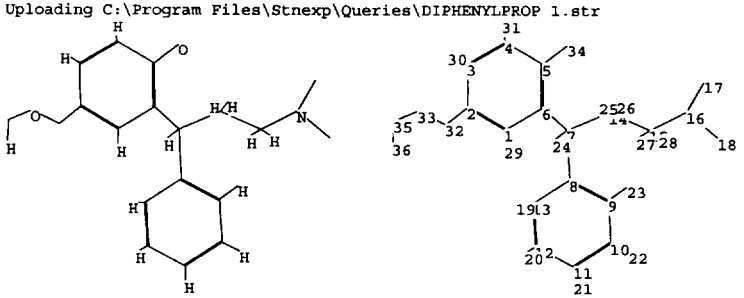
Welcome to STN International! Enter x:x

LOGINID:ssspta1623zct

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'REGISTRY' AT 07:52:11 ON 24 NOV 2004
FILE 'REGISTRY' ENTERED AT 07:52:11 ON 24 NOV 2004
COPYRIGHT (C) 2004 American Chemical Society (ACS)

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.84	1.05

=>
Uploading C:\Program Files\Stnexp\Queries\DIPHENYLPROP 1.str

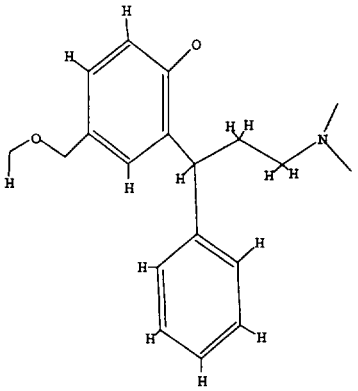


chain nodes :
7 14 15 16 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 36
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13
ring/chain nodes :
17 18 35
chain bonds :
1-29 2-32 3-30 4-31 5-34 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20
13-19 14-15 14-25 14-26 15-16 15-27 15-28 16-17 16-18 32-33 33-35 35-36
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13
exact/norm bonds :
5-34 15-16 16-17 16-18 32-33 33-35
exact bonds :
1-29 2-32 3-30 4-31 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20 13-19
14-15 14-25 14-26 15-27 15-28 35-36
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS
27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS
35:CLASS 36:CLASS

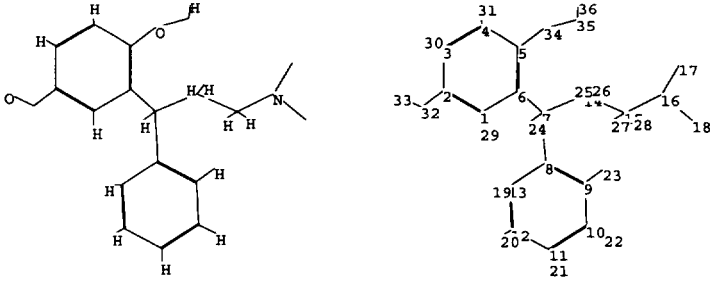
L3 STRUCTURE UPLOADED

=> D L3
L3 HAS NO ANSWERS
L3 STR



Structure attributes must be viewed using STN Express query preparation.

=>
Uploading C:\Program Files\Stnexp\Queries\DIPHENYLPROP 2.str



chain nodes :
7 14 15 16 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 36
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13
ring/chain nodes :
17 18 35
chain bonds :
1-29 2-32 3-30 4-31 5-34 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20
13-19 14-15 14-25 14-26 15-16 15-27 15-28 16-17 16-18 32-33 34-35 35-36

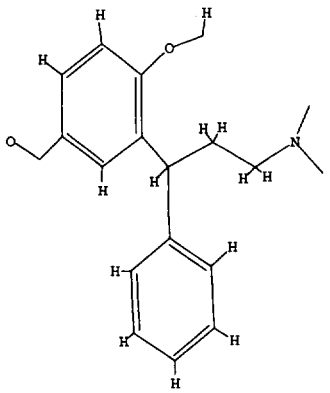
STN SEARCH TRANSCRIPT 10/17/05 1623

ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13
exact/norm bonds :
5-34 15-16 16-17 16-18 32-33 34-35
exact bonds :
1-29 2-32 3-30 4-31 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20 13-19
14-15 14-25 14-26 15-27 15-28 35-36
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS
27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS
35:CLASS 36:CLASS

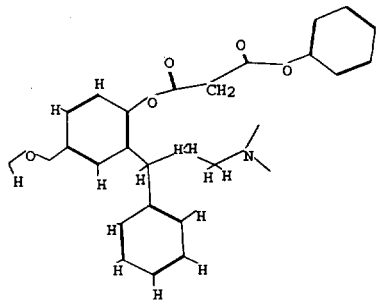
L4 STRUCTURE UPLOADED

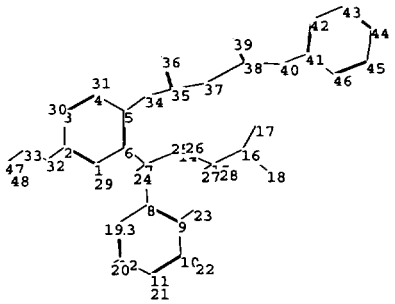
=> D L4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

=>
Uploading C:\Program Files\Stnexp\Queries\DIPHENYLPROP 3.str





chain nodes :
7 14 15 16 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 36
37 38 39 40 47 48
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13 41 42 43 44 45 46
ring/chain nodes :
17 18 35
chain bonds :
1-29 2-32 3-30 4-31 5-34 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20
13-19 14-15 14-25 14-26 15-16 15-27 15-28 16-17 16-18 32-33 33-47 34-35
35-36 35-37 37-38 38-39 38-40 40-41 47-48
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 41-42 41-46
42-43 43-44 44-45 45-46
exact/norm bonds :
5-34 15-16 16-17 16-18 32-33 33-47 34-35 35-36 38-39 38-40 40-41
exact bonds :
1-29 2-32 3-30 4-31 6-7 7-8 7-14 7-24 9-23 10-22 11-21 12-20 13-19
14-15 14-25 14-26 15-27 15-28 35-37 37-38 47-48
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 41-42 41-46
42-43 43-44 44-45 45-46

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS
27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS
35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS 41:Atom 42:Atom
43:Atom 44:Atom 45:Atom 46:Atom 47:CLASS 48:CLASS

L5 STRUCTURE UPLOADED

=> D L5
L5 HAS NO ANSWERS
L5 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> S L3 SSS FULL
FULL SEARCH INITIATED 07:54:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 197 TO ITERATE

100.0% PROCESSED 197 ITERATIONS 25 ANSWERS
SEARCH TIME: 00.00.01

L6 25 SEA SSS FUL L3

=> S L4 SSS FULL
FULL SEARCH INITIATED 07:54:15 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 83 TO ITERATE

100.0% PROCESSED 83 ITERATIONS 24 ANSWERS
SEARCH TIME: 00.00.01

L7 24 SEA SSS FUL L4

=> S L5 SSS FULL
FULL SEARCH INITIATED 07:54:22 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 23 TO ITERATE

100.0% PROCESSED 23 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L8 0 SEA SSS FUL L5

=> S L6 OR L7 OR L8
L9 44 L6 OR L7 OR L8

=> FILE CAPLUS
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 467.52 467.73

FILE 'CAPLUS' ENTERED AT 07:54:39 ON 24 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 24 Nov 2004 VOL 141 ISS 22
FILE LAST UPDATED: 23 Nov 2004 (20041123/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

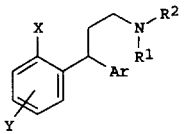
=> S L9
L10 8 L9

=> D 1-8 IBIB ABS HITSTR

L10 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:51413 CAPLUS
DOCUMENT NUMBER: 136:102178
TITLE: Preparation of 3,3-diarylpropylamines via hydroformylation-amination of diarylethenes in presence of a transition metal catalyst
INVENTOR(S): Donsbach, Martin; Eilbracht, Peter; Buss, Christian; Schmidt, Andreas
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004399	A1	20020117	WO 2001-EP7803	20010706
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10033016	A1	20020124	DE 2000-10033016	20000707
EP 1299342	A1	20030409	EP 2001-962840	20010706
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004502748	T2	20040129	JP 2002-509068	20010706
US 2004034080	A1	20040219	US 2003-332290	20030714
US 6809225	B2	20041026		

PRIORITY APPLN. INFO.: DE 2000-10033016 A 20000707
WO 2001-EP7803 W 20010706
OTHER SOURCE(S): CASREACT 136:102178; MARPAT 136:102178
GI



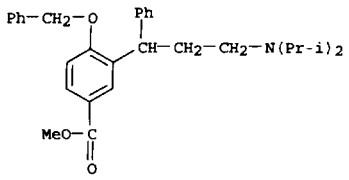
I

AB The invention relates to a novel method for producing 3,3-diarylpropylamines I [Ar = (un)substituted aryl; X = (un)substituted OH; Y = Cl, Br, I, CN, CH2OR, CHO, CO2H, CO2R; R = alkyl, aryl; R1, R2 = alkyl, cycloalkyl; NR1R2 = heterocyclic] by hydroformylation/hydrocarbonylation and subsequent reductive amination using a transition metal catalyst. Thus, 5,2-Me(HO)C6H3COPh was methylated and methylenated with MeP+Ph3 Br- to give 5,2-Me(MeO)C6H3CPh:CH2 which was treated with (Me2CH)2NH, CO, and H in presence of Rh(acac)(CO)2 and Bu3P to give 85% 5,2-Me(MeO)C6H3CHPhCH2CH2N(CHMe2)2.

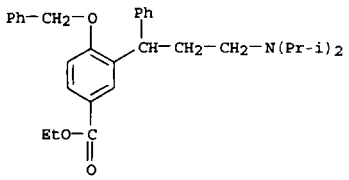
IT **286930-05-0P 389068-25-1P**

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 3,3-diarylpropylamines via hydroformylation-amination of diarylethenes in presence of a transition metal catalyst)

RN 286930-05-0 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)



RN 389068-25-1 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, ethyl ester (9CI) (CA INDEX NAME)



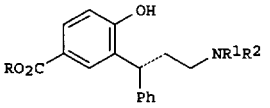
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:923742 CAPLUS
DOCUMENT NUMBER: 136:37403
TITLE: Shortened synthesis of 3,3-diarylpropylamine derivatives
INVENTOR(S): Meese, Claus
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

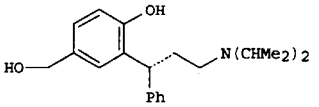
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096279	A1	20011220	WO 2001-EP6577	20010611
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, 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, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10028443	C1	20020529	DE 2000-10028443	20000614
CA 2412047	AA	20011220	CA 2001-2412047	20010611
EP 1289929	A1	20030312	EP 2001-947355	20010611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001011266	A	20031216	BR 2001-11266	20010611
JP 2004503520	T2	20040205	JP 2002-510423	20010611
NZ 521265	A	20040625	NZ 2001-521265	20010611
ZA 2002007204	A	20030523	ZA 2002-7204	20020909
US 2003212292	A1	20031113	US 2002-297778	20021209
US 6809214	B2	20041026		
NO 2002005967	A	20021212	NO 2002-5967	20021212

PRIORITY APPLN. INFO.: DE 2000-10028443 A 20000614
WO 2001-EP6577 W 20010611

OTHER SOURCE(S): CASREACT 136:37403; MARPAT 136:37403
GI



I

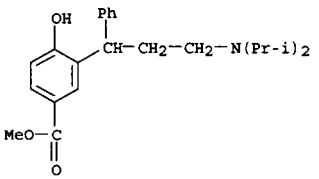


II

AB 3,3-Diarylpropylamines I [R = H, alkyl; R1, R2 = alkyl] are prepared by reaction of RO2CC6H4OH-4 with PhCH:CHCO2H to give a 2-oxo-4-phenyl-3,4-dihydrobenzopyran-6-carboxylate which is resolved via its cinchonidine salt, the (R)-isomer hydrolyzed to the acid which is reesterified, reduced to the benzopyranol, and subjected to aminolysis to give I. I [R = Me, R1, R2 = CHMe2], thus obtained, was then reduced to the benzyl alc. II.

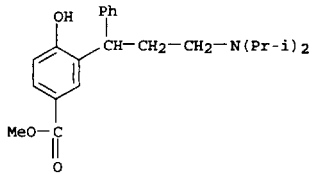
IT **214601-16-8P 380636-45-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(shortened synthesis of 3,3-diarylpropylamine derivs.)

RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)



RN 380636-45-3 CAPLUS

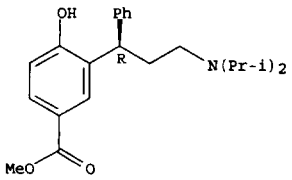
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **214601-17-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(shortened synthesis of 3,3-diarylpropylamine derivs.)
RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:449738 CAPLUS
DOCUMENT NUMBER: 135:61141
TITLE: Preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters.
INVENTOR(S): Meese, Claus
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

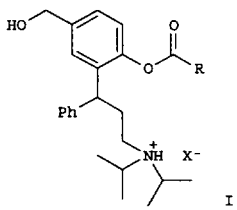
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19955190	A1	20010621	DE 1999-19955190	19991116
DE 29923134	U1	20000803	DE 1999-29923134	19991116
CA 2389749	AA	20010525	CA 2000-2389749	20001115
WO 2001035957	A1	20010525	WO 2000-EP11309	20001115
WO 2001035957	A3	20011227		

W: 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, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001026667	A5	20010530	AU 2001-26667	20001115
BR 2000015610	A	20020730	BR 2000-15610	20001115
EP 1230209	A2	20020814	EP 2000-989857	20001115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003514018	T2	20030415	JP 2001-537950	20001115
ZA 2002003315	A	20030725	ZA 2002-3315	20020425
NO 2002002314	A	20020515	NO 2002-2314	20020515

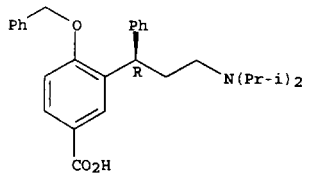
PRIORITY APPLN. INFO.: DE 1999-19955190 IA 19991116
WO 2000-EP11309 W 20001115

OTHER SOURCE(S): MARPAT 135:61141
GI



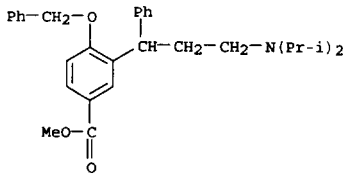
AB Title compds. [I; R = alkyl, cycloalkyl, (substituted) Ph; X- = residue of a physiol. acceptable (in)organic acid], were prepared Thus, (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate (II) (preparation given) in 2-butanone was treated with fumaric acid under warming to give 83.1% II.hydrogen fumarate.
IT **156755-33-8 286930-05-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)
RN 156755-33-8 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

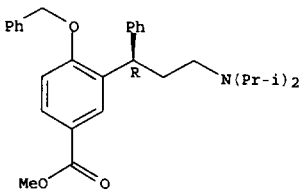
RN 286930-05-0 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)



IT **156755-35-0P 156755-37-2P 214601-16-8P 214601-17-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)

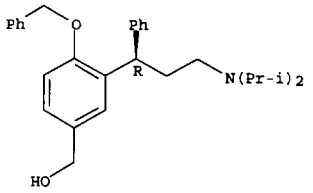
RN 156755-35-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

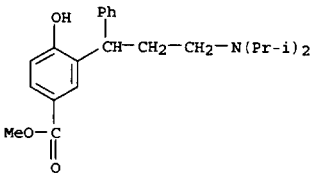


RN 156755-37-2 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

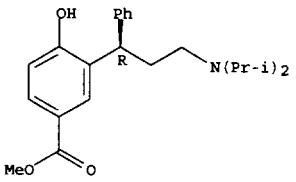


RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)



RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

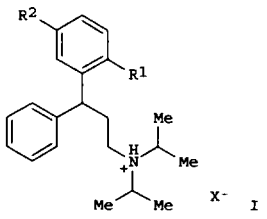
Absolute stereochemistry. Rotation (-).



L10 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:533448 CAPLUS
DOCUMENT NUMBER: 133:155419
TITLE: Stable salts of novel derivatives of 3,3-diphenylpropylamines
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Gebrauchsmusterschrift, 37 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 29923134	U1	20000803	DE 1999-29923134	19991116

DE 19955190 A1 20010621 DE 1999-19955190 19991116
PRIORITY APPLN. INFO.: DE 1999-19955190 IA 19991116
OTHER SOURCE(S): MARPAT 133:155419
GI

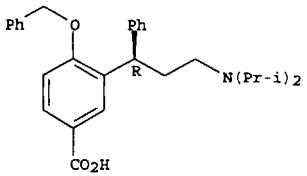


AB 3,3-Diphenylpropylamine salts I [R1 = RCO2; R = C1-6 alkyl, C3-10 cycloalkyl, (substituted) Ph; R2 = CH2OH; X = inorg. or organic acid] are prepared for use as prodrugs of agents for treatment of urinary incontinence and other spasmogenic disorders. I show improved absorption through biol. membranes and improved metabolic patterns and are easily crystallized I are prepared from I free base (R1 = PhCH2O, R2 = CO2Me) by debenzylation, reduction, acylation, and combination with HX. Thus, R-(-)-I-HCl (R1 = PhCH2O, R2 = CO2H) was esterified by refluxing in acidic MeOH, the ester was reduced with LiAlH4, the resulting carbinol was reduced with Raney Ni/H2, and the product [R-(+)-I free base, R = CHMe2] was converted to its H fumarate salt by heating with equimolar fumaric acid in 2-butanone; the salt was crystallized by addition of cyclohexanone and cooling to 0°.

IT **156755-33-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stable salts of novel derivs. of diphenylpropylamines)

RN 156755-33-8 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

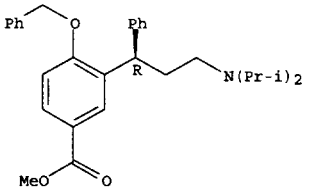


● HCl

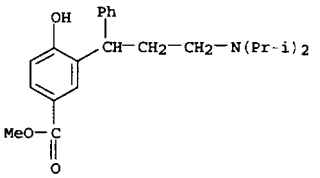
IT **156755-35-0P 214601-16-8P 214601-17-9P 286930-05-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stable salts of novel derivs. of diphenylpropylamines)

RN 156755-35-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

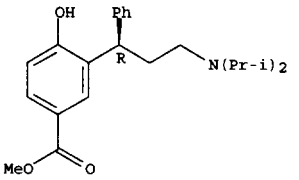


RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

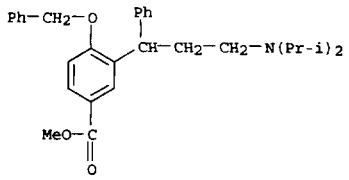


RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 286930-05-0 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)



L10 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:736261 CAPLUS
DOCUMENT NUMBER: 131:336818
TITLE: Preparation of 3,3-diphenylpropylamines as antimuscarinic agents.
INVENTOR(S): Sparf, Bengt; Meese, Claus O.
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

APPLICANTS

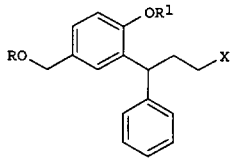
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 957073	A1	19991117	EP 1998-108608	19980512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2328920	AA	19991118	CA 1999-2328920	19990511
WO 9958478	A1	19991118	WO 1999-EP3212	19990511
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, 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, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941412	A1	19991129	AU 1999-41412	19990511
AU 748057	B2	20020530		
BR 9910406	A	20010109	BR 1999-10406	19990511
EP 1077912	A1	20010228	EP 1999-924929	19990511
EP 1077912	B1	20020703		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200003319	T2	20011221	TR 2000-200003319	19990511
AT 220056	E	20020715	AT 1999-924929	19990511
EP 1254890	A1	20021106	EP 2002-13481	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NZ 507487	A	20021126	NZ 1999-507487	19990511
PT 1077912	T	20021129	PT 1999-924929	19990511
ES 2181443	T3	20030216	ES 1999-924929	19990511
RU 2199525	C2	20030227	RU 2000-125813	19990511
JP 2003519079	T2	20030617	JP 2000-548284	19990511
ZA 2000005728	A	20010305	ZA 2000-5728	20001017
NO 2000005669	A	20010111	NO 2000-5669	20001110
US 6713464	B1	20040330	US 2001-700094 ✓	20010102 PARENT APP'N
US 2004186061	A1	20040923	US 2004-766263	20040127

THIS APP'N

PRIORITY APPLN. INFO.:

EP 1998-108608	A	19980512
EP 1999-924929	A3	19990511
WO 1999-EP3212	W	19990511
US 2001-700094	A1	20010102

OTHER SOURCE(S): MARPAT 131:336818
GI



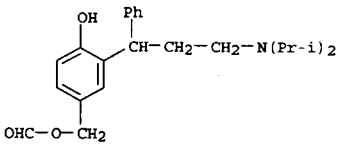
I

AB Title compds. (I; R = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, CHO, Ac, propionyl, isobutyryl, aminocarbonyl, aminosulfonyl, MeO2C, etc.; R1 = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, phenylalkyl; Z = NR8R9; R8, R9 = hydrocarbyl; NR8R9 = atoms to form a ring; with a proviso), were prepared as antimuscarinic agents (no data). Thus, 4-bromophenol, cinnamoyl chloride, and Et3N were stirred 18 h in CH2Cl2 to give 99.8% 3-phenylacrylic acid 4-bromophenyl ester. This was refluxed 2 h with HOAc/H2SO4 to give 43.8% 6-bromo-4-phenylchroman-2-one. The latter was refluxed with benzyl bromide, K2CO3, and NaI in acetone/MeOH to give 102.1% crude Me 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionate, which was stirred with LiAlH4 in THF to give 96.3% 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol. This was stirred with tosyl chloride and pyridine in CH2Cl2 for 18 h to give 93.6% tosylate ester, which was refluxed 97 h with diisopropylamine in MeCN to give 77.9% [3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]diisopropylamine. The latter was converted in several steps to 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, which was acylated to give I.

IT **250214-62-1P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3,3-diphenylpropylamines as antimuscarinic agents)

RN 250214-62-1 CAPLUS

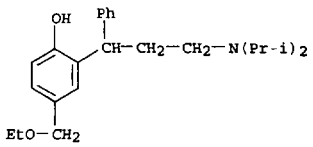
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, α-formate (9CI) (CA INDEX NAME)



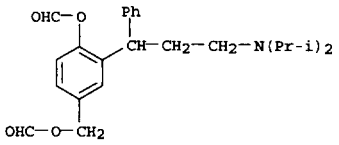
IT **214601-24-8P 250214-51-8P 250214-57-4P 250214-58-5P 250214-69-8P 250214-70-1P 250214-71-2P 250214-72-3P 250214-73-4P 250214-74-5P 250214-78-9P 250214-79-0P 250214-85-8P 250214-86-9P 250214-87-0P 250214-94-9P 250215-00-0P 250215-01-1P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3,3-diphenylpropylamines as antimuscarinic agents)

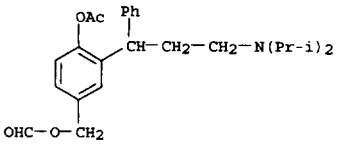
RN 214601-24-8 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)-(9CI) (CA INDEX NAME)



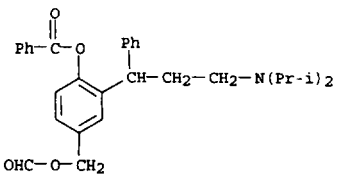
RN 250214-51-8 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(formyloxy)-, formate (ester) (9CI) (CA INDEX NAME)



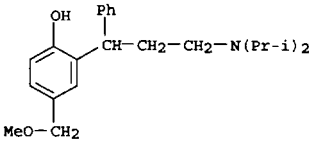
RN 250214-57-4 CAPLUS
CN Benzenemethanol, 4-(acetyloxy)-3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-, formate (ester) (9CI) (CA INDEX NAME)



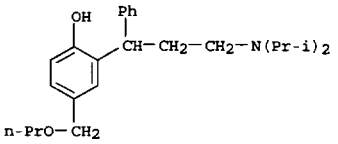
RN 250214-58-5 CAPLUS
CN Benzenemethanol, 4-(benzoyloxy)-3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-, formate (ester) (9CI) (CA INDEX NAME)



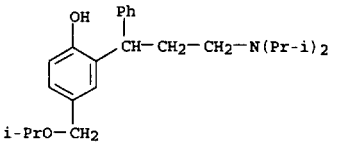
RN 250214-69-8 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(methoxymethyl)-(9CI) (CA INDEX NAME)



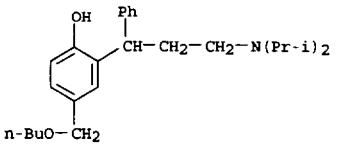
RN 250214-70-1 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(propoxymethyl)-(9CI) (CA INDEX NAME)



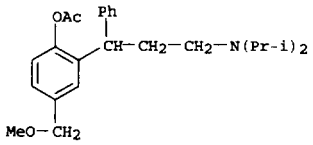
RN 250214-71-2 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-[(1-methylethoxy)methyl]- (9CI) (CA INDEX NAME)



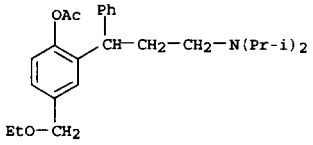
RN 250214-72-3 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(butoxymethyl)-(9CI) (CA INDEX NAME)



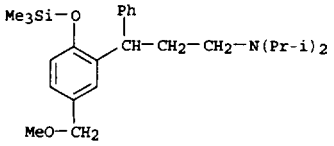
RN 250214-73-4 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(methoxymethyl)-, acetate (ester) (9CI) (CA INDEX NAME)



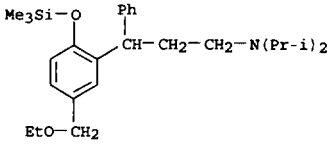
RN 250214-74-5 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)-, acetate (ester) (9CI) (CA INDEX NAME)



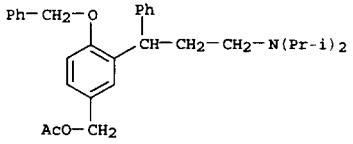
RN 250214-78-9 CAPLUS
CN Benzenepropanamine, 5-(methoxymethyl)-N,N-bis(1-methylethyl)-γ-phenyl-2-[(trimethylsilyl)oxy]- (9CI) (CA INDEX NAME)



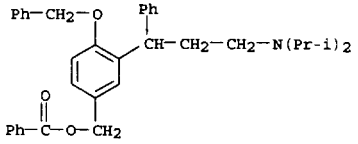
RN 250214-79-0 CAPLUS
CN Benzenepropanamine, 5-(ethoxymethyl)-N,N-bis(1-methylethyl)-γ-phenyl-2-[(trimethylsilyl)oxy]- (9CI) (CA INDEX NAME)



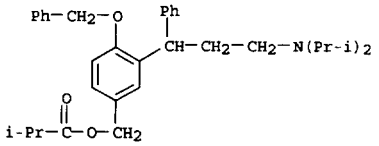
RN 250214-85-8 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, acetate (ester) (9CI) (CA INDEX NAME)



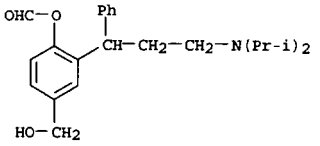
RN 250214-86-9 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, benzoate (ester) (9CI) (CA INDEX NAME)



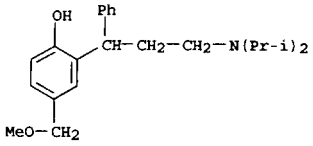
RN 250214-87-0 CAPLUS
CN Propanoic acid, 2-methyl-, [3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)phenyl]methyl ester (9CI) (CA INDEX NAME)



RN 250214-94-9 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(formyloxy)- (9CI) (CA INDEX NAME)

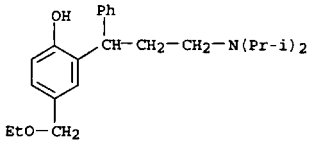


RN 250215-00-0 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(methoxymethyl)-, hydrochloride (9CI) (CA INDEX NAME)



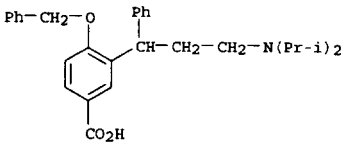
● HCl

RN 250215-01-1 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)-, hydrochloride (9CI) (CA INDEX NAME)



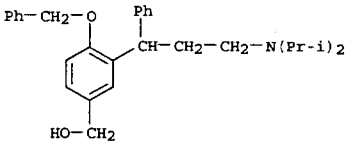
● HCl

IT **250214-38-1P 250214-39-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 3,3-diphenylpropylamines as antimuscarinic agents)
RN 250214-38-1 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 250214-39-2 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

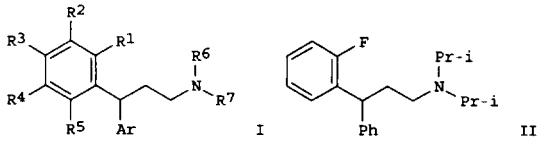
L10 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:682217 CAPLUS
DOCUMENT NUMBER: 129:316029
TITLE: Novel 3-aryl-3-phenylpropanamines with anticholinergic activity, their use in the treatment of urinary incontinence, and their preparation
INVENTOR(S): Johansson, Rolf; Haraldsson, Martin; Ringberg, Erik; Vagberg, Jan; Beierlein, Katarina; Emond, Rikard; Sjoberg, Birger
PATENT ASSIGNEE(S): Pharmacia and Upjohn AB, Swed.
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

NOT PRIOR ART

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843942	A1	19981008	WO 1998-SE556	19980326
W: 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, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9802478	A	19981008	ZA 1998-2478	19980324
CA 2284977	AA	19981008	CA 1998-2284977	19980326
AU 9867552	A1	19981022	AU 1998-67552	19980326
AU 739186	B2	20011004		
BR 9808069	A	20000308	BR 1998-8069	19980326
EP 1019358	A1	20000719	EP 1998-912864	19980326
EP 1019358	B1	20030507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001522355	T2	20011113	JP 1998-541548	19980326
AT 239693	E	20030515	AT 1998-912864	19980326
PT 1019358	T	20030930	PT 1998-912864	19980326
ES 2199433	T3	20040216	ES 1998-912864	19980326
TW 555735	B	20031001	TW 1998-87105376	19980409
NO 9904438	A	19991126	NO 1999-4438	19990913
MX 9908862	A	20000228	MX 1999-8862	19990927
US 6313132	B1	20011106	US 1999-381868	19990927

PRIORITY APPLN. INFO.: SE 1997-1144 A 19970327
WO 1998-SE556 W 19980326

OTHER SOURCE(S): MARPAT 129:316029
GI



I

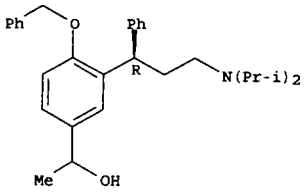
II

AB The invention relates to novel compds. I [wherein R1 = H, OH, alkyl, alkoxy, CF3, amino, alkanoylamino, alkanoyloxy, halo, hydroxyalkyl; R2, R3 = H, OH, alkyl, alkoxy, hydroxyalkyl, halo, carbamoyl, etc.; R4 = (un)substituted alkyl or amino, CHO, CO2H, NO2, cyano, N3, alkoxy, and may also be H, Me, OMe, etc. under some circumstances; R5 = H, halo, alkyl; Ar = (un)substituted (hetero)aryl; R6, R7 = hydrocarbyl with optional OH groups or O bridge(s), and may form a ring; with several provisos], their salts with physiol. acceptable acids, their racemic mixts., and the individual enantiomers. The compds. have anticholinergic activity, and in particular are of use in the treatment of urinary incontinence. Sixty synthetic examples are given, and approx. 90 compds. (including free bases and salts) were prepared and/or claimed. For instance, Wittig-type reaction of (EtO)2P(O)CH2CON(Pr-iso)2 with 2-fluorobenzophenone, followed by hydrogenation of the formed olefin and reduction of the amide with LiAlH4, gave after acidification, title compound II.HCl. In a test for inhibition of carbachol-induced contraction of isolated guinea pig bladder strips, II had a KB value of 10 nM, and other compds. had values ranging from 1.18 nM to 3315 nM.

IT **214601-51-1P 214601-52-2P 214601-53-3P**
214601-61-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of arylphenylpropanamines as anticholinergic agents)

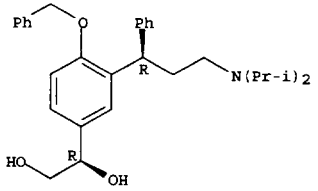
RN 214601-51-1 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-α-methyl-4-(phenylmethoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



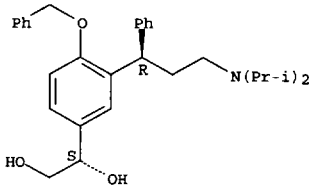
RN 214601-52-2 CAPLUS
CN 1,2-Ethanediol, 1-[3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)phenyl]-, (1R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

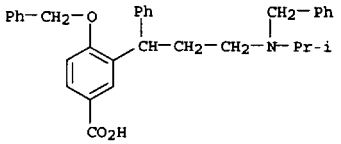


RN 214601-53-3 CAPLUS
CN 1,2-Ethanediol, 1-[3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)phenyl]-, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



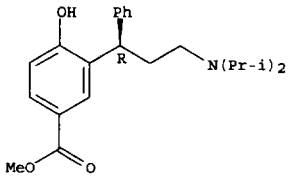
RN 214601-61-3 CAPLUS
CN Benzoic acid, 3-[3-[(1-methylethyl)(phenylmethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)- (9CI) (CA INDEX NAME)



IT **214600-45-0P 214600-58-5P 214601-16-8P**
214601-17-9P 214601-24-8P 214602-05-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of arylphenylpropanamines as anticholinergic agents)

RN 214600-45-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

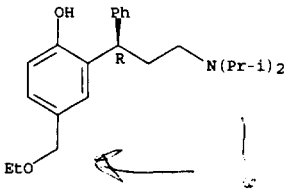
Absolute stereochemistry. Rotation (-).



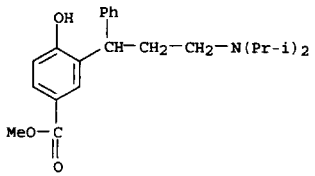
● HCl

RN 214600-58-5 CAPLUS
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

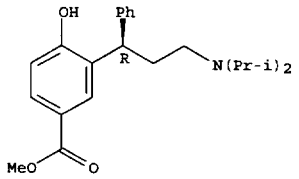


RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

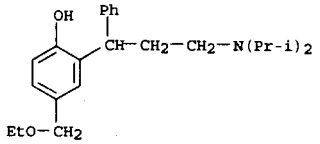


RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 214601-24-8 CAPLUS
CN Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)- (9CI) (CA INDEX NAME)

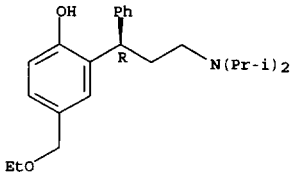


RN 214602-05-8 CAPLUS
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(ethoxymethyl)-, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 214600-58-5
CMF C24 H35 N O2

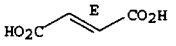
Absolute stereochemistry.



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



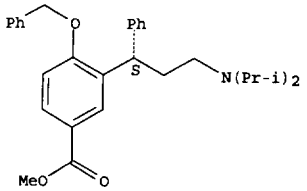
IT **156755-34-9**
RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of arylphenylpropanamines as anticholinergic agents)

RN 156755-34-9 CAPLUS

CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:393013 CAPLUS

DOCUMENT NUMBER: 129:156415

TITLE: Biotransformation of tolterodine, a new muscarinic receptor antagonist, in mice, rats, and dogs

AUTHOR(S): Andersson, Stig H. G.; Lindgren, Anders; Postlind, Hans

CORPORATE SOURCE: Department of Drug Metabolism, Pharmacia & Upjohn AB, Uppsala, S-751 82, Swed.

SOURCE: Drug Metabolism and Disposition (1998), 26(6), 528-535
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

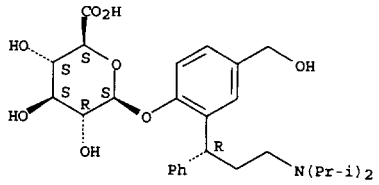
AB Tolterodine is intended for the treatment of urinary urge incontinence and other symptoms associated with an overactive bladder. The in vivo metabolism of 14C-labeled tolterodine was investigated in rats, mice, and dogs by anal. of blood and urine samples, whereas in vitro metabolism studies were performed by incubation of [14C]tolterodine with mouse, rat, dog, and human liver microsomes in the presence of NADPH. Tolterodine was extensively metabolized in vivo. Mice and dogs showed similar metabolite patterns, which correlated well with that observed in humans. In these species, tolterodine was metabolized along 2 different pathways, with the more important being the stepwise oxidation of the 5-Me group to yield the 5-hydroxymethyl metabolite of tolterodine and then, via the aldehyde, the 5-carboxylic acid metabolite. The other pathway involved dealkylation of the nitrogen. In the subsequent phase II metabolism, tolterodine and the metabolites were conjugated with glucuronic acid to various degrees. Rats had a more extensive metabolism and a markedly different metabolite pattern, with metabolites also being formed by hydroxylation of the nonsubstituted benzene ring. Gender differences were also observed, with male rats showing more extensive metabolism than females. Incubation of [14C]tolterodine yielded 5 metabolites with rat microsomes and 3 metabolites with mouse, dog, and human microsomes. The 5-hydroxymethyl metabolite of tolterodine and N-dealkylated tolterodine were major metabolites in all incubations, representing 83-99% of total metabolism Although the extent of metabolism varied among the species, the metabolic profiles were similar. Rat liver microsomes also formed metabolites hydroxylated in the nonsubstituted benzene ring. Thus, the metabolism of tolterodine in mice and dogs corresponds to that observed in humans, whereas rats have a different metabolite pattern.

IT **210573-52-7 210573-53-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tolterodine biotransformation in mice, rats, dogs and humans)

RN 210573-52-7 CAPLUS

CN β-D-Glucopyranosiduronic acid, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl (9CI) (CA INDEX NAME)

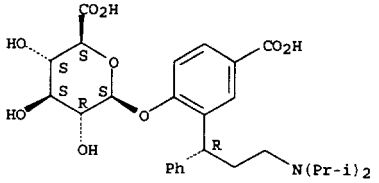
Absolute stereochemistry.



RN 210573-53-8 CAPLUS

CN β-D-Glucopyranosiduronic acid, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-carboxyphenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:508197 CAPLUS

DOCUMENT NUMBER: 121:108197

TITLE: Preparation of 3,3-diphenylpropylamines and their use

INVENTOR(S): Johansson, Rolf Arne; Moses, Pinchas; Nilverbant, Lisbeth; Sparf, Bengt Aake

PATENT ASSIGNEE(S): Kabi Pharmacia AB, Swed.

SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

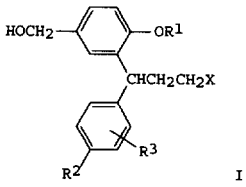
102(b)

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411337	A1	19940526	WO 1993-SE927	19931105
W: AU, CA, FI, HU, JP, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2148827	AA	19940526	CA 1993-2148827	19931105

AU 9454380	A1	19940608	AU 1994-54380	19931105
AU 672458	B2	19961003		
EP 667852	A1	19950823	EP 1993-924876	19931105
EP 667852	B1	19980408		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08503208	T2	19960409	JP 1994-511977	19931105
JP 3343256	B2	20021111		
HU 72742	A2	19960528	HU 1995-1329	19931105
AT 164828	E	19980415	AT 1993-924876	19931105
ES 2117155	T3	19980801	ES 1993-924876	19931105
FI 9502179	A	19950505	FI 1995-2179	19950505
NO 9501775	A	19950505	NO 1995-1775	19950505
US 5559269	A	19960924	US 1995-432113	19950505
US 5686464	A	19971111	US 1996-684638	19960722
PRIORITY APPLN. INFO.:			SE 1992-3318 A	19921106
			WO 1993-SE927 W	19931105
			US 1995-432113 A3	19950505

OTHER SOURCE(S): MARPAT 121:108197
GI



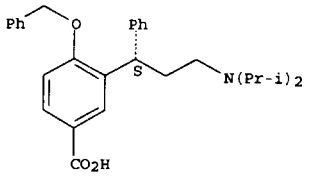
I

AB Title compds. I (R1 =H, Me; R2, R3 = H, Me, MeO, HO, H2NCO, H2NSO2, halo; X = R4R5N wherein R4, R5 = non-aromatic hydrocarbyl and which together contain at least three carbon atoms, or R4R5N = heterocyclyl), salts, optical isomers, racemic mixture and individual enantiomers are useful as anticholinergics. P-Br-C6H4OH, PhCH:CHCO2H, AcOH and H2SO4 were refluxed to give 6-bromo-4-phenyl-3,4-dihydrocoumarin which was converted in 4 steps to N,N-diisopropyl3-(2-benzyloxy-5-brophenyl)-3-phenylpropylamine (II). II was resolved to the (-)-isomer and converted in 4 steps to (-)-I [R1 = PhCH2, R2 = R3 = H, X = (Me2CH)2N].(-) mandelate salt (III). In tests for anticholinergic effect, III produced a dose-dependent inhibition of the acetylcholine-induced effect on the bladder which was about 10 times more efficient than that of a prior art analog.

IT **156755-32-7P 156755-33-8P 156755-34-9P**
156755-35-0P 156755-36-1P 156755-37-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of anticholinergics)

RN 156755-32-7 CAPLUS
CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

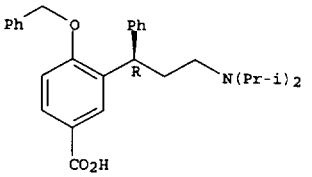
Absolute stereochemistry. Rotation (+).



● HCl

RN 156755-33-8 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

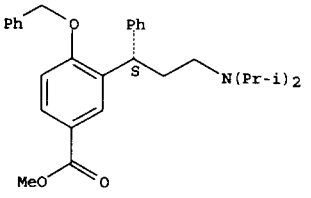
Absolute stereochemistry. Rotation (-).



● HCl

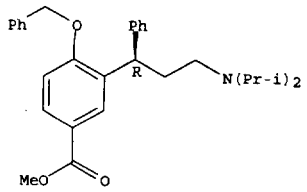
RN 156755-34-9 CAPLUS
CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



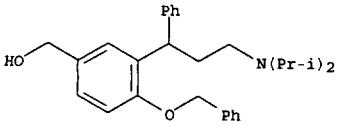
RN 156755-35-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



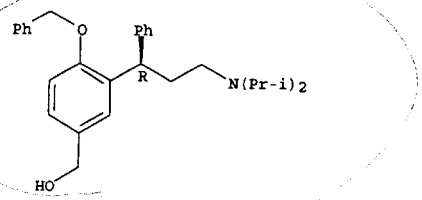
RN 156755-36-1 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 156755-37-2 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



=>
Connection closed by remote host

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	55647-C (45107)	3433

21874 7590 11/29/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-49* is/are pending in the application.

4a) Of the above claim(s) *30,33-35,38,40,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29,31,41 and 42* is/are rejected.

7)☒ Claim(s) *32,36,37,39,43 and 46-49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/700,094.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 28, 29, 31, 32, 36, 37, 39, 41-43 and 46-49, all in part) in the reply filed on 27 October 2004, to the Requirement for Restriction mailed 28 September 2004, is acknowledged.

The examiner notes that the alternative identity for R and R' in Group I of the Requirement for Restriction was erroneously set forth. Group I also includes those compounds where one or both of R and R' are allyl.

Claims 30, 33-35, 38, 40, 44 and 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 specifies in the preamble that a method of producing ethers is provided, while the process step recited is that of an esterification reaction. Thus, the preamble is repugnant to the actual process claimed. Claim 41 has not been further examined on the merits in this Office action.

Claim 42 also specifies in the preamble that a method of producing ethers is provided, while it is clear from a reading of the claim that the actual process steps

produce many compounds in addition to ethers. For example, reactants (c) and (f) would produce esters, reactant (e) would produce a carbamate or carbonate.

Claim 42 is further indefinite because the term "suitable hydroxy reagents" is not understood to be a term of art. The specification does not provide sufficient definition of what compounds belong to this class of reagent. Page 32 suggests that these reagents include alcohols, but no further description of the assumedly broad class of "suitable hydroxy reagents" is given. Thus, the full scope of what applicants intend "suitable hydroxy reagent" to encompass is unclear. Replacement of the phrase with "suitable alcohol" would be sufficient to overcome at least this ground of rejection.

Claim 42 has not been further examined on the merits in this office action because it is unclear what compounds are produced by the process when the above pointed-out reactants are employed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,686,464 (Johanssen et al).

In column 9, lines 4-16, the preparation of the compound (-)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxymethyl)-3-phenylpropylamine is disclosed.

The (+) isomer is also prepared in an analogous manner.

These compounds are compounds according to claims 28, 29 and 31 where R' (claims 28 and 29) or R^{11} (claim 31) is benzyl, R (claims 28 and 29) or R^{10} (claim 31) is hydrogen and X in claim 28 is diisopropylamine.

Claim Objections

Claim 32 is objected to because non-elected subject matter is recited.

The first five named species in claim 32 are within the elected group and are allowable, however.

Claims 36 and 37 are objected to because non-elected subject matter is recited.

Claims 36 and 37 would be allowable if amended to delete non-elected subject matter. A composition comprising allowable compounds of claims 32, 36 and 37 (as specified in claim 39) and methods as specified in claims 46-49, commensurate in scope with the allowable compounds would be allowable as well.

There is no disclosure of nor any suggestion to make a compound according to claims 32 (first five species), 36 or 37 in the prior art.

Claims 39, 43 and 46-49 are objected to because they depend from a rejected base claim and also recite non-elected subject matter, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and to delete non-elected subject matter.

Comments

Although not applicable as prior art, US 6,313,132 (Johansson et al) discloses the second named species in instant claim 32, and includes a claim to this species in claim 19 of that patent (it is the 9th named species).

It appears that US 6,313,132 and the instant application do not have any inventors in common and are not commonly owned.

Applicant is on notice that a potential case of interference exists.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 6:15am to 2:45pm, Monday from 6:15am to 1:45pm and Friday from 6:15am to 3:45pm (EST). If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-2717.

zt

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

Index of Claims

Application No.	Applicant(s)
10/766,263	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	11/2004
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	
	14	
	15	
	16	
	17	
	18	
	19	
	20	
	21	
	22	
	23	
	24	
	25	
	26	
	27	
	28	√
	29	√
	30	N
	31	√
	32	O
	33	N
	34	N
	35	N
	36	O
	37	O
	38	N
	39	O
	40	N
	41	√
	42	√
	43	O
	44	N
	45	N
	46	O
	47	O
	48	O
	49	O
	50	

Claim		Date
Final	Original	
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

Claim		Date
Final	Original	
	101	
	102	
	103	
	104	
	105	
	106	
	107	
	108	
	109	
	110	
	111	
	112	
	113	
	114	
	115	
	116	
	117	
	118	
	119	
	120	
	121	
	122	
	123	
	124	
	125	
	126	
	127	
	128	
	129	
	130	
	131	
	132	
	133	
	134	
	135	
	136	
	137	
	138	
	139	
	140	
	141	
	142	
	143	
	144	
	145	
	146	
	147	
	148	
	149	
	150	

Search Notes

Application No.	Applicant(s)	
10/766,263	MEESE ET AL.	
Examiner	**Art Unit**	
Zachary C. Tucker	1624	

SEARCHED

Class	Subclass	Date	Examiner
560 (VII')	194	11/24/04	ZT
564	316		
514	548; 648	11/24/04	ZT

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
EAST USPAT, USPG PUB, EPO, JPO; DERWENT CLASS AND SUBCLASS CROSSED W/	11/24/04	ZT
"ANTIMUSCARINIC" OR "TOLTERODINE"		
STN - REGISTRY STRUCTURE SEARCH CROSSED ANSWER SET IN CAPLUS	11/24/04	ZT
(TRANSCRIPT ATTACHED.)		
PALM - INVENTOR NAMES SEARCH	11/24/04	ZT

AMENDMENT TRANSMITTAL LETTER

Docket No. 55647CON(45107)

Application No.	Filing Date	Examiner	Art Unit
10/766,263-Conf. #3433	January 27, 2004	Z. C. Tucker	1624

Applicant(s): Claus Meese et al.

Invention: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims		- 20 =		x	
Independent Claims		- 3 =		x	
Multiple Dependent Claims (check if applicable)	☐				
Other fee (please specify):					
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					0.00

☒ Large Entity ☐ Small Entity

☒ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

☐ A check in the amount of $ _____ to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge and credit Deposit Account No. 04-1105 as described below. A duplicate copy of this sheet is enclosed.

☒ Credit any overpayment.

☒ Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

Christine C. O'Day
Attorney Reg. No.: 38,256

Dated: February 28, 2005

EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 492 339 561 US, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: February 28, 2005 Signature: _____ (Elisabeth Dunkle)

479898

3-2-05 IFW

Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese, et al.		
U.S.S.N.:	10/766,263	Art Unit:	1624
FILED:	January 27, 2004	Examiner:	Tucker, Z. C.
FOR:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

Applicants are in receipt of the Office Action dated November 29, 2004. Please consider the remarks set forth below and amend the above-identified application as indicated.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 11 of this paper.

AMENDMENT TRANSMITTAL LETTER

Docket No. 55647CON(45107)

Application No.	Filing Date	Examiner	Art Unit
10/766,263-Conf. #3433	January 27, 2004	Z. C. Tucker	1624

Applicant(s): Claus Meese et al.

Invention: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims		- 20 =		x	
Independent Claims		- 3 =		x	
Multiple Dependent Claims (check if applicable)	☐				
Other fee (please specify):					
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					0.00

☒ Large Entity ☐ Small Entity

☒ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

☐ A check in the amount of $ _____ to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge and credit Deposit Account No. 04-1105 as described below. A duplicate copy of this sheet is enclosed.

☒ Credit any overpayment.

☒ Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

Christine C. O'Day
Attorney Reg. No.: 38,256

Dated: February 28, 2005

EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 492 339 561 US, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: February 28, 2005 Signature: _____ (Elisabeth Dunkle)

479898

3-2-05 IFW

Docket No. 55647-C (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese, et al.		
U.S.S.N.:	10/766,263	Art Unit:	1624
FILED:	January 27, 2004	Examiner:	Tucker, Z. C.
FOR:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

Applicants are in receipt of the Office Action dated November 29, 2004. Please consider the remarks set forth below and amend the above-identified application as indicated.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

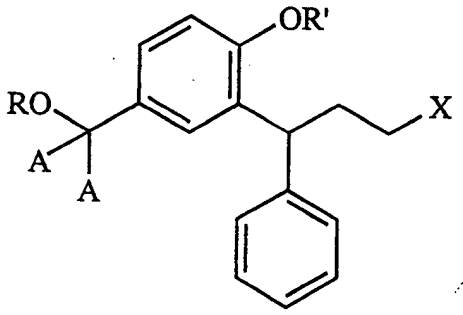
Remarks begin on page 11 of this paper.

Listing of claims:

This listing of claims will replace all previously filed listings.

1-49. (Cancelled).

50. (New): A 3,3-Diphenylpropylamine having the formula I:



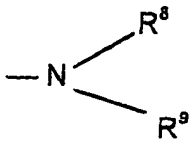
Formula I

wherein R and R' are independently

hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, or allyl;

with the proviso that at least one of R' and R is not hydrogen, and the proviso that R' is not methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia



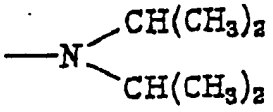
Formula Ia

wherein R^8 and R^9 represent C_1-C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

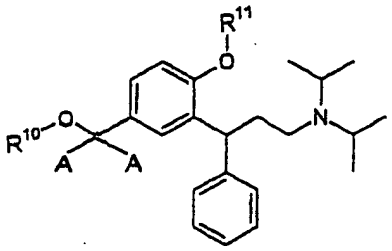
A represents hydrogen (^1H) or deuterium (^2H), and

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

51. (New): The 3,3-Diphenylpropylamine of claim 50, wherein X is



52. (New): A 3,3-Diphenylpropylamine having the formula VI:



Formula VI

wherein A represents hydrogen (^1H) or deuterium (^2H), and

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

wherein one of R^{10} or R^{11} is selected from C_1-C_6 alkyl, allyl, or benzyl, and the other represents hydrogen,

with the proviso that R^{11} is not methyl or benzyl when R^{10} is hydrogen, and R^{10} is not ethyl when R^{11} is hydrogen.

53. (New): The 3,3-Diphenylpropylamine of claim 52 selected from the group consisting of:

(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-methoxymethyl-phenol,

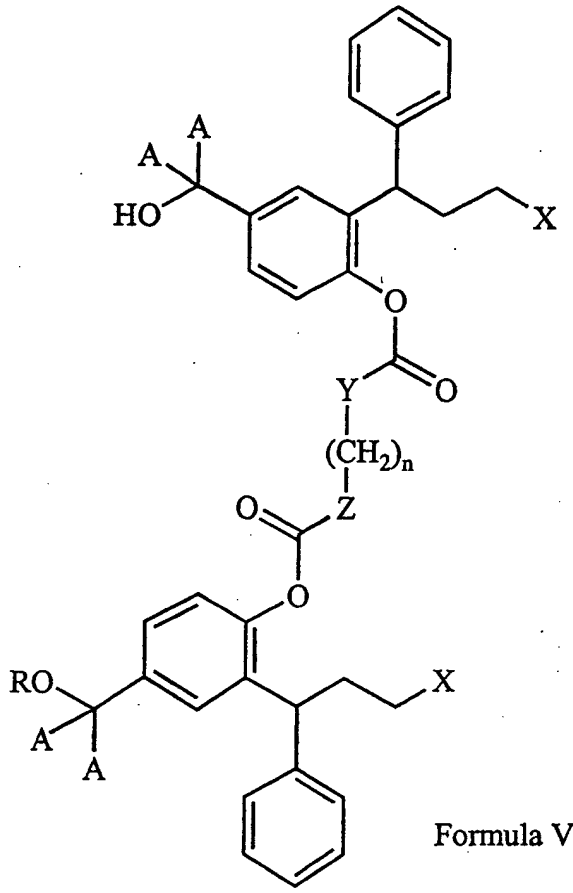
(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-ethoxymethyl-phenol,

(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-propoxymethyl-phenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,

(±)-2-(3-diisopropylamino-l-phenylpropyl)-4-butoxymethyl-phenol.

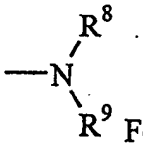
54. (New): A 3,3-Diphenylpropylamine having the formula VII':



Formula VII'

wherein R is C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, or allyl;

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

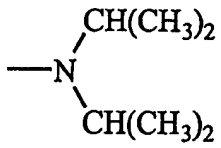
Y and Z independently represent O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12, and

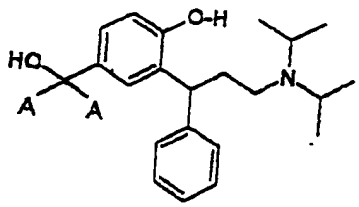
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

55. (New): The 3,3-Diphenylpropylamines of claim 54, wherein X is



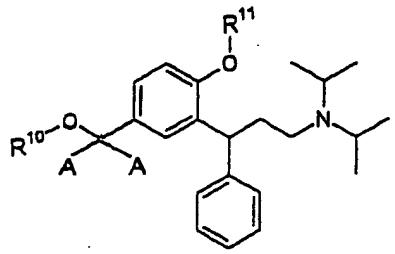
56. (New): A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 50-55 and a pharmaceutically acceptable carrier.

57. (New): A process for the production of ethers according to claim 52, wherein R^{11} is hydrogen, which comprises reacting a compound of the formula



with an alcohol R^{10}-OH in the presence of a catalyst.

58. (New): A process for the preparation of ethers of formula VI:



Formula VI

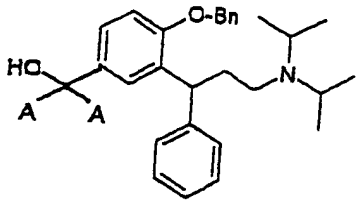
wherein A represents hydrogen (^1H) or deuterium (^2H), and

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

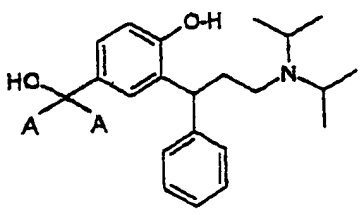
wherein one of R^{10} or R^{11} is selected from C_1-C_6 alkyl, allyl, or benzyl, and the other represents hydrogen,

with the proviso that R^{11} is not methyl or benzyl when R^{10} is hydrogen, and R^{10} is not ethyl when R^{11} is hydrogen;

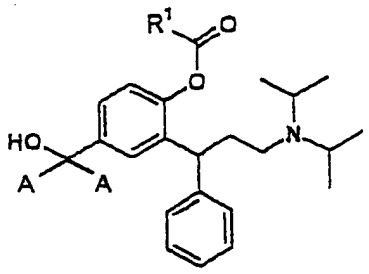
wherein the process comprises acid or base treatment, in the presence of at least one alcohol selected from $R^{10}OH$ and $R^{11}OH$, of a compound selected from



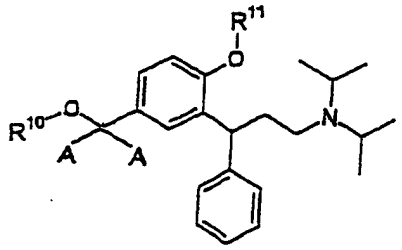
(a)



(b)

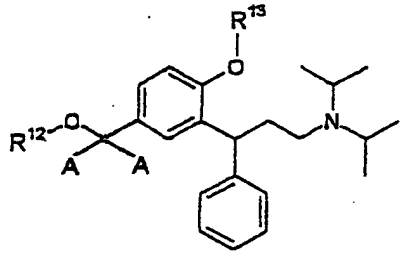


(c) Formula II



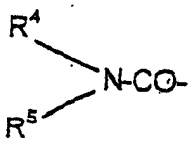
(d) Formula VI

wherein R^{10} is hydrogen,



(e) Formula VII

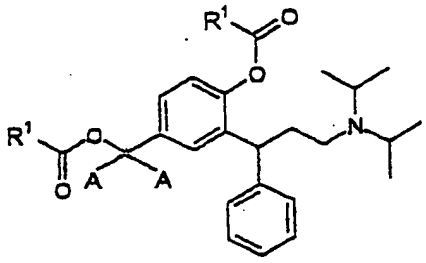
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



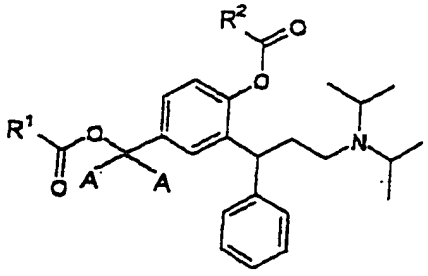
wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted

aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen, and

(f) benzylic acylates selected from

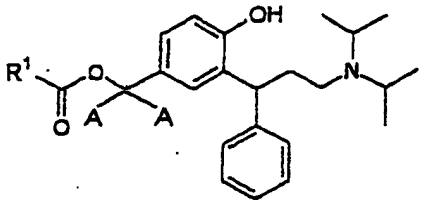


Formula III



Formula IV

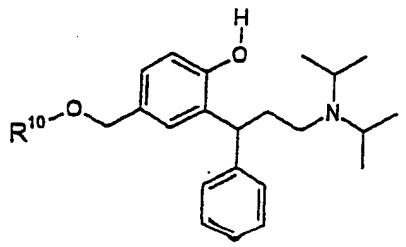
and



Formula V

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl, and R^2 represents hydrogen, C_1-C_6 alkyl or phenyl, with the proviso that R^1 and R^2 are not identical.

59. (New): A process for the preparation of ethers of formula VI according to claim 52, which comprises treating a compound of the formula



with an alkylating agent selected from alkyl halides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

60. (New): A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 50-55.

61. (New): A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim 56 effective to diminish or eliminate symptoms of the disease.

62. (New): The method according to claim 61 wherein the disease is urinary incontinence.

63. (New): The method according to claim 62 wherein the mammal is a human.

REMARKS

Claims 1-49 have been cancelled and new claims 50-63 have been added. No new matter is presented by virtue of the within amendment. For instance, the within amendment is submitted, in significant part, to exclude non-elected subject matter and correct minor informalities. Support for the newly presented claims is found throughout the specification and claims as originally filed.

Amendment of any claim herein is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action. Such amendments are being made in an effort to expedite prosecution of the present application. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject mattered.

At the outset, the undersigned attorney appreciates the recent opportunity to discuss the present application with the Examiner. As part of that discussion, it was agreed that "allyl" is properly included as a possible R/R' value in part a) of claim 28 (new claim 50). While no definitive agreement was reached, the opportunity for combination of certain of the remaining groups of claims set forth in the Restriction Requirement dated September 28, 2004, was discussed in connection with a further (as yet, unfiled) continuation application.

Referring now to the Office Action, Applicants appreciate the indication of allowable subject matter, i.e., that claims 32, 36, 37, 43, and 46-49 (corresponding to new claims 53, 54, 55, 59, and 60-63) would be allowable if amended to overcome the objections. In particular, the Office Action states that claims 32, 36, 37, 43, and 46-49 are merely objected to as containing non-elected subject matter, and being dependent on an objected base claim.

Favorable reconsideration of the present application is respectfully requested in light of the within amendments and remarks which follow.

35 U.S.C. §112, Second Paragraph Rejection

Claims 41 (new claim 57) and 42 (new claim 58) have been rejected under 35 U.S.C. §112, second paragraph. The Office Action alleges that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Office Action asserts that claim 41 specifies in the preamble that a method of producing ethers is provided, while the process step recited is that of an esterification reaction. Therefore, it is alleged that the preamble is repugnant to the actual process claimed.

Applicants have cancelled claim 41 and rewritten the subject matter thereof in new claim 57. The recitation of "esterification catalyst" has been replaced by "catalyst." Support can be found in the specification as filed, at least on page 32, wherein "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." No recitation of an esterification catalyst is indicated for the incorporation of an ether functionality onto a benzylic alcohol. Therefore, the rejection is obviated and Applicants respectfully request its withdrawal.

The Office Action further asserts that claim 42 specifies in the preamble that a method of producing ethers is provided, while the process step recited would produce many compounds in addition to ethers. For example, reactants (c) and (f) would produce esters, reactant (e) would produce a carbamate or carbonate.

Applicants have cancelled claim 42 and have added new claim 58. Claim 58 recites the process for the preparation of compounds of formula VI wherein one of R^{10} or R^{11} is H. For example, reactant (c) will lose the ester functionality in the presence of an acid or base and a suitable alcohol can then be incorporated as $R^{10}O$- or $R^{11}O$-. The

corresponding formula VI compound would include the suitable alcohol at either R^{10} or R^{11} with the other R^{10} or R^{11} being H. Applicants respectfully request withdrawal of the rejection.

The Office Action goes on to assert that in claim 42 (new claim 58) recitation of "suitable hydroxy reagents" is not understood to be a term of art, and that the specification does not provide sufficient definition of what compounds belong to this class of reagent. However, replacement of the phrase with "suitable alcohol" would be sufficient to overcome at least this ground of the rejection.

Applicants have replaced "suitable hydroxy reagents" with "at least one alcohol selected from $R^{10}OH$ and $R^{11}OH$" in claim 58, thus obviating the rejection. Applicants submit that the amendment provided *supra* more particularly describes the subject matter of the instant invention. Applicants respectfully request withdrawal of the rejection.

The Office Action further asserts that claim 42 (new claim 58) has not been further examined because it is unclear what compounds are produced by the process when the above pointed-out reactants are employed.

Applicants submit that claim 58 is directed towards the synthesis of compounds of formula VI. An example of this process is exemplified on page 75 of the specification as example (e), which discloses the synthesis of compounds of formula VI. Applicants therefore respectfully request withdrawal of the rejection.

35 U.S.C. §102(b) Rejection

Claims 28, 29, and 31 (new claims 50, 51, and 52) stand rejected as being anticipated by US 5,686,464 (Johanssen et al.), when R'/R^{11} is benzyl, R/R^{10} is hydrogen, and X is diisopropylamine.

Applicants submit that the proviso in claim 50 (and subsequent dependent claim 51), effectively removes the compound disclosed by Johanssen. Support for the proviso can be found at least in claim 28, and claim 1 as originally filed. The same proviso is currently presented for formula VI in new claim 52. Support for the proviso of formula VI can be found at least in former claim 31. Applicants respectfully request withdrawal of the rejection.

Claim Objections

Claim 32 (new claim 53) was objected to because non-elected subject matter is recited therein. The Office Action indicates that the first five named species in claim 32 are within the elected group and are allowable.

New claim 53 recites those compounds that fall within the elected subject matter. The objection is thus obviated and Applicants respectfully request its withdrawal.

As a matter of formality, Applicants reserve the right to pursue the non-elected subject matter of this application in one or more further continuation or divisional applications.

Claims 36 and 37 (new claims 54 and 55) were objected to because non-elected subject matter is recited therein. The Office Action indicates that claims 36 and 37 would be allowable if amended to delete that non-elected subject matter. Further, claims 39 and 46-49 (new claims 56 and 60-63) would be allowable as well if amended to exclude non-elected subject matter.

Applicants submit that new claim 54 excludes non-elected subject matter. Applicants aver that claim 54 is in condition for allowance. Further, new claims 55, 56, and 60-63 are in condition for allowance as they depend, at least in part, from claim 54. Applicants respectfully request withdrawal of the objection.

It is alleged that claims 39, 43 and 46-49 (new claims 56, 59, and 60-63) are objected to because they depend from a rejected base claim and also recite non-elected subject matter, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and to delete non-elected subject matter.

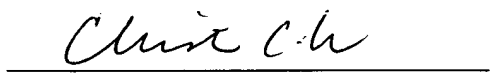
Applicants aver that new claims 56 and 60-63 are in condition for allowance (*vide supra*). New claim 59 depends from claim 52, and is presented in a manner which recites only the elected subject matter. Therefore, the objection to claim 59 is obviated and Applicants indicate that claim 59, as presented, is in condition for allowance.

CONCLUSION

In view of the above amendments and the arguments presented, reconsideration and withdrawal of all rejections are respectfully solicited.

Applicants have addressed the objections and rejections provided in the outstanding Office Action, and it is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



Christine C. O'Day (Reg. 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444

Date: February 28, 2005

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10766263

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	22	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	82 minus 20=	* 62
INDEPENDENT CLAIMS	4 minus 3 =	* 1
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	385.00	OR	BASIC FEE	770.00
XS 9=		OR	XS18=	1116.00
X43=		OR	X86=	86.00
+145=		OR	+290=	290.00
TOTAL		OR	TOTAL	2262

2-2805

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 38	Minus	** 82	= —
Independent	* 7	Minus	*** 4	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
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
XS 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
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=	
X43=		OR	X86=	
+145=		OR	+290=	
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.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

SERIAL NO. 10/766,263 | FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1ST AMENDMENT		AFTER 2ND AMENDMENT	
	IND	DEP	IND	DEP	IND	DEP
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28	1					
29		1				
30		1				
31	1					
32		1				
33		1				
34		1				
35	1					
36	1					
37		1				
38		1				
39		11				
40		11				
41		1				
42		1				
43		1				
44		1				
45		1				
46		11				
47		11				
48		11				
49		11				
50			1			
TOTAL IND.	4					
TOTAL DEP.	28					
TOTAL CLAIMS	32					

			AFTER 1ST AMENDMENT		AFTER 2ND AMENDMENT	
	IND	DEP	IND	DEP	IND	DEP
51				1		
52			1			
53				1		
54			1			
55				1		
56				6		
57				1		
58			1			
59				1		
60				6		
61				6		
62				6		
63						
64						
65						
66						
67						
68						
69						
70						
71						
72						
73						
74						
75	1					
76						
77						
78						
79						
80						
81						
82						
83						
84						
85						
86						
87						
88						
89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.			3			
TOTAL DEP.			35			
TOTAL CLAIMS			38			

PTO-1360 (Rev. 07/1(3-03))

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21874 7590 05/10/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/10/2005

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	55647-C (45107)	3433

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	08/10/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 12/04) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax **(703) 746-4000**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21874 7590 05/10/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	55647-C (45107)	3433

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	08/10/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-548000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above. NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	55647-C (45107)	3433

21874 7590 05/10/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/10/2005

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 12/04) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *50-63*.

3. ☒ The drawings filed on *27 January 2004* are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *09/700,094* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The following amendments to the specification are necessary to render the instant application compliant with 37 CFR 1.77 (arrangement and contents of the specification) and 37 CFR 1.78(a)(1)(iv)(i) (cross-reference to related applications), and reflect the arrangement and contents of the specification of the parent application, 09/700,094. Applicants' preliminary amendment filed 27 January 2004 included a cross-reference to the parent application, serial number 09/700,094, but that application had not yet issued as a patent. The cross-reference to the parent application is re-stated hereinbelow, with added reference to the patent number of the parent application.

IN THE SPECIFICATION –

At page 1, under the title of the application, insert the following paragraph:

"The present application is a Continuation Application of USSN 09/700,094, filed January 2, 2001, now US Patent 6,713,464, which in turn claimed the priority benefit of PCT/EP99/03212, filed May 11, 1999."

Followed by the heading:

--BACKGROUND OF THE INVENTION--

At page 3, line 17 (before the paragraph that begins "It is an object...") insert the heading:

--SUMMARY OF THE INVENTION--

At page 4, starting at line 4 (BEFORE the paragraph beginning that begins "According to the present invention..." insert the following paragraph and headings:

--BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** shows the formation of the active metabolite from different prodrugs by human liver S 9(%) in 1 hour.

DETAILED DESCRIPTION OF THE INVENTION--

end of amendments

Response to Amendment

As requested in the correspondence from applicants filed 28 February 2005, which is in reply to the Office action mailed 29 November 2004 (hereinafter "previous Office action"), claims 28-49 have been cancelled and new claims 50-63 added.

Election/Restrictions

Applicants have presented a new claim set, numbered 50-63, wherein no subject matter other than as was set forth in Group I of the Requirement for Restriction mailed 28 September 2004 is recited.

As was indicated in the previous Office action, page 2, in the section headed "Election/Restrictions," R and/or R' = "allyl" is part of Group I, the elected group. This was confirmed in a telephone conversation between applicants' counsel and the examiner after the previous Office action was mailed.

Status of Claim Rejections - 35 USC § 112

In the previous Office action, claims 41 and 42 were rejected under the second paragraph of 35 U.S.C. 112, because, it was asserted, the preamble of those claims was repugnant to the actual process described.

Claims 41 and 42 have been cancelled, mooting the rejection of those claims.

Claim Rejections - 35 USC § 102

In the previous Office action, claims 28, 29 and 31 were rejected under 35 U.S.C. 102(b) as being anticipated by US 5,686,464 (Johansson et al).

Claims 28, 29 and 31 have been cancelled, mooting the rejection of those claims.

Claim Objections

In the previous Office action, claims 32, 36 and 37 were objected to for recitations of non-elected subject matter, but indicated as allowable, insofar as the elected subject matter was concerned.

In the previous Office action, claims 39, 43 and 46-49 were objected to as depending from a rejected base claim, and also for recitation of non-elected subject matter, and indicated as allowable insofar as the elected subject matter was concerned.

All claim objections are rendered moot by cancellation of all previously pending claims.

As indicated above in the section headed "Election/Restrictions," the new claim set is free of the non-elected subject matter.

Allowable Subject Matter

Claims 50-63 are allowed.

The following is an examiner's statement of reasons for allowance:

No disclosure rendering obvious or anticipating compounds according to instant claims 50-55, the composition according to claim 56, the process according to claims 57-59 or the methods according to claims 60-63 is found in the prior art.

The previously stated rejections under 35 U.S.C. 102(b) of claims 28, 29 and 31 were erroneous, because the proviso in those claims, which proviso excludes those compounds wherein R' is not benzyl when R is hydrogen. This was inadvertently overlooked in the preparation of the previous Office action.

Also, the same proviso excludes those compounds wherein R is ethyl when R' is hydrogen. This is important because, as indicated in the previous office action, at least one such compound is claimed in US 6,313,312 (Johansson et al). No such compound is claimed in the instant application.

The closest prior art with respect the instantly claimed compounds is the afore-cited US 5,686,464 (Johansson et al), and

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-872-9306, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

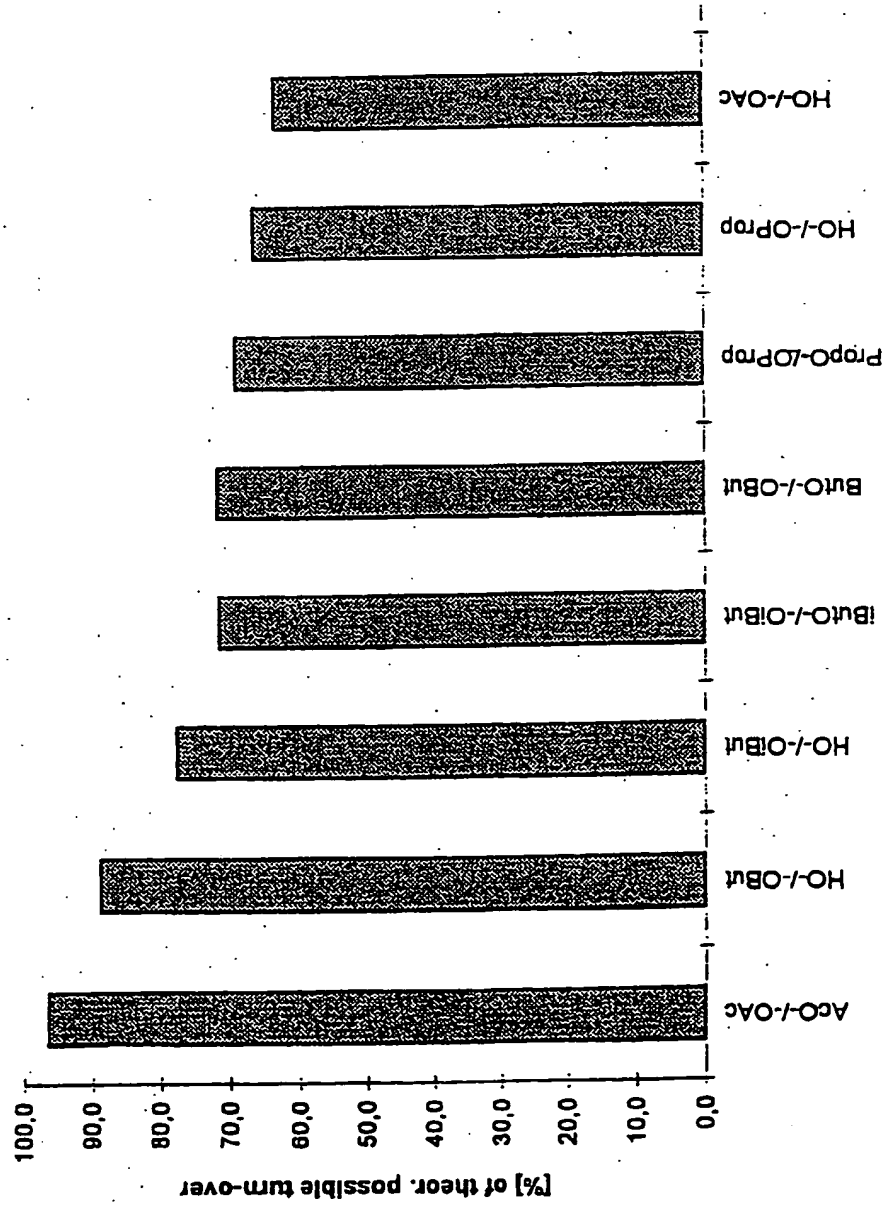
For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

zt

JAMES O WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

FIG. 1

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



Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
514	548	514	648
INTERNATIONAL CLASSIFICATION		560	194
A01N	37/02	564	316
A01N	37/06		
A61K	31/225		
C07C	69/34		
C07C	211/00		

Zachary C. Tucker (ZACHARY C. TUCKER) 20-APR-05
(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
(Primary Examiner) (Date)

Total Claims Allowed: 14

O.G. Print Claim(s)	O.G. Print Fig.
1 (60)	1

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11		41		71		101		131		161		191
	12		42		72		102		132		162		192
	13		43		73		103		133		163		193
	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
	17		47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
	23		53		83		113		143		173		203
	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/766,263	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim Final	Claim Original	Date 4/1/2005	Claim Final	Claim Original	Date 4/1/2005	Claim Final	Claim Original	Date
	1		2	51	11		101	
	2		3	52	|		102	
	3		4	53	|		103	
	4		5	54	|		104	
	5		6	55	|		105	
	6		7	56	|		106	
	7		8	57	|		107	
	8		9	58	|		108	
	9		10	59	|		109	
	10		11	60	|		110	
	11		12	61	|		111	
	12		13	62	↓		112	
	13		14	63	11		113	
	14			64			114	
	15			65			115	
	16			66			116	
	17			67			117	
	18			68			118	
	19			69			119	
	20			70			120	
	21			71			121	
	22			72			122	
	23			73			123	
	24			74			124	
	25			75			125	
	26			76			126	
	27			77			127	
	28			78			128	
	29			79			129	
	30			80			130	
	31			81			131	
	32			82			132	
	33			83			133	
	34			84			134	
	35			85			135	
	36			86			136	
	37			87			137	
	38			88			138	
	39			89			139	
	40			90			140	
	41			91			141	
	42			92			142	
	43			93			143	
	44			94			144	
	45			95			145	
	46			96			146	
	47			97			147	
	48			98			148	
	49			99			149	
1	50	11		100			150	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 34

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKE NO.
10/766,263	01/27/2004 RULE	514	1624	55647-C (45107)

APPLICANTS

Claus Meese, Monheim, GERMANY;

Bengt Sparf, Trangsund, SWEDEN;

** CONTINUING DATA **********

This application is a CON of 09/700,094 01/02/2001 PAT 6,713,464
which is a 371 of PCT/EP99/03212 05/11/1999

** FOREIGN APPLICATIONS **********

EUROPEAN PATENT OFFICE (EPO) 98108608.5 05/12/1998

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 06/16/2004

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDE
☒ yes ☐ no	COUNTRY	DRAWING	CLAIMS	CLAIMS
35 USC 119 (a-d) conditions met ☒ yes ☐ no ☐ Met after Allowance	GERMANY	1	22	4
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS
21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON , MA
02205

TITLE
Novel derivatives of 3,3-diphenylpropylamines

FILING FEE	FEES: Authority has been given in Paper	☐ All Fees
RECEIVED 2262	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time ☐ 1.18 Fees (Issue) ☐ Other _____

h e e e e e c

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/766,263	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

- UPDATE -

SEARCHED

Class	Subclass	Date	Examiner
560	194	4/20/05	ZT
564	316		
514	548		
	648		

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
PALM - INVENTOR NAMES SEARCH UPDATED	4/20/05	ZT
EAST - USPAT, USPG-PUB, EPO, JPO, DERWENT CLASSES AND SUBCLASSES CROSSED W/ "TOLTERODINE" OR "PROPYLAMINE" OR "DIPHENYLPROPYLAMINE(S)"	4/20/05	ZT
STN - REVIEW OF TRANSCRIPT FROM REGISTRY/CAPLUS SEARCH OF 11/24/04	4/20/05	ZT

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner
560	194	4/20/05	ZT
564	316		
514	548, 648		

AUG 15 2005

PATENT & TRADEMARK OFFICE

PART B FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Stop ISSUE FEE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 Or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

Current correspondence address (Note: Legibly mark-up with any corrections or use Block 1)

Customer No. 26646 7590 Mailing Date 05/10/2005

Kenyon & Kenyon
ONE BROADWAY
NEW YORK 10004

08/16/2005 WABDELR3 00000055 110600 10766263
01 FC:1501 1400.00 DA
02 FC:1504 300.00 DA
03 FC:8021 80.00 DA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its on certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's Name) Joseph A. Coppola
(Signature)
(Date) August 10, 2005

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	12961/46102	3433

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	08/10/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C.	1624	514-548000

1. Change of correspondence address or indication of "Fee Address" (37 CRF 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indicating form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed

1 Kenyon & Kenyon
2 ____
3 ____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when assignment has been previously submitted to the USTPO or is being submitted under separate cover. Completion of this form is NOT a substitute fir filing as assignment.

NAME OF ASSIGNEE	(B)RESIDENCE: (CITY and STATE OR COUNTRY)
1) SCHWARZ PHARMA AG	Alfred-Nobel-Strasse 10, D-40789 Monheim, Federal Republic of Germany

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:
☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):
☐ A Check. in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached
☒ The Director is hereby authorized by charge the required fee(s), or credit any government, to Deposit Account Number 11-0600 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27 (g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

Authorized Signature: Joseph A. Coppola Date: AUG. 10, 2005

Typed or printed name: Joseph A. Coppola Registration No.: 38,413

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		
REVOCATION OF PRIOR POWER OF ATTORNEY and APPOINTMENT OF NEW POWER OF ATTORNEY BY ASSIGNEE and 3.73(b) STATEMENT		Docket Number: **12961/46102**
Application Number: **10/766,263**	Filing Date: **January 27, 2004**	
Invention Title: **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s): **Claus MEESE et al.**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SCHWARZ PHARMA AG, as assignee of the entire interest of the above-identified patent by virtue of executed assignments as indicated below, hereby revokes all powers of attorney previously given and appoints the practitioners associated with Kenyon & Kenyon's customer number:

26646

to prosecute and transact all business in the Patent and Trademark Office connected therewith.

SCHWARZ PHARMA AG, is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 10/766,263 filed on January 27, 2004 which is a continuation of U.S. Patent Application Serial No. 09/700,094 filed on January 02, 2001, now U.S. Patent No. 6,713,464 issued on March 30, 2004 by virtue of the following chain of title from the inventor(s) to the current assignee as shown below:

1. From: Claus Meese, and

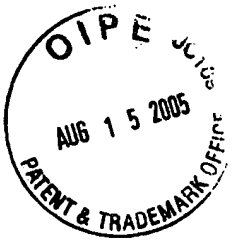
   From: Bengt Sparf

   To: Schwarz Pharma AG

The document was recorded on January 11, 2001 in the United States Patent and Trademark Office at

Reel 011443 Frame 0478, or for which a copy thereof is attached.

Please send all correspondence and direct telephone calls to:



Joseph A. Coppola, Esq.
Kenyon & Kenyon
One Broadway
New York, NY 10004
Customer No: 26646

The undersigned is authorized to act on behalf of the assignee:

SCHWARZ PHARMA AG

Date: August 10, 2005

By: Thielgen

Name: THIELGEN

Title: CFO

Date: August 10, 2005

By:

Name: BAUMANN

Title: Member of the Executive Board

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

REQUEST FOR CONTINUED EXAMINATION (RCE)
TRANSMITTAL FORM (37 C.F.R. § 1.114)

DOCKET NO.	APPLICATION SERIAL NO.	EXAMINER	ART UNIT
12961/46102	**10/766,263**	**Zachary C. TUCKER**	**1624**

INVENTOR(S): **Claus MEESE et al.**

Address to:
U.S. Patent and Trademark Office
Customer Window, Mail Stop 313(c)
Randolph Building
Alexandria, VA 22314

This is a **request for continued examination** under 37 C.F.R. § 1.114 (RCE) of pending application Serial No. **10/766,263**, filed on **January 27, 2004**, entitled **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES.**

The following constitute the submission **required** by 37 C.F.R. § 1.114(a) and is attached:

_____ Amendment
__X__ Information Disclosure Statement and Form PTO-1449
_____ Drawing Changes
_____ Other Submission: _____

1. The filing fee for this RCE and the required amendment/submission is calculated below. The fee below is calculated based on the status of the claims after the entry of the attached amendment/submission. The fee for any new additional claims is included with this RCE, the fee for previously entered additional claims having already been paid.

	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT NUMBER EXTRA*	RATE ($) PER CLAIM	FEE ($)
BASIC FEE						790.00
TOTAL CLAIMS	14	20	89	0	x $50.00	0.00
INDEPENDENT CLAIMS	4	3	5	0	x $200.00	0.00
MULTIPLE DEPENDENT CLAIM	1	0	1	0	$360.00	0.00
				*Number extra must be zero or larger	TOTAL	790.00
	If Applicant is a small entity under 37 C.F.R. §§ 1.9 and 1.27, then divide total fee by 2, and enter amount here.				SMALL ENTITY TOTAL	

08/24/2005 JADD01 00000052 110600 10766263
01 FC:1801 790.00 DA

2. Please charge the required RCE and submission filing fee of **$790.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11–0600**.

3. The Commissioner is hereby authorized to charge payment of the fees, including any additional fees required, associated with this communication or arising during the pendency of this application, or to credit any overpayment, to the deposit account of **Kenyon & Kenyon**, deposit account number **11–0600**.

4. A duplicate copy of this transmittal form is enclosed.

Dated: August 22, 2005

By: Respectfully submitted,

Joseph A. Coppola (Reg. No. 38,413)
KENYON & KENYON
One Broadway
New York, New York 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NO. 26646

office petition IPW DAC $

12961/46102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Claus MEESE, et al.
Serial No.	:	10/766,263
Filed	:	January 27, 2004
For	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
Examiner	:	Zachary C. TUCKER
Group Art Unit	:	1624
Confirmation No.	:	3433

U.S. Patent and Trademark Office
Customer Window, Mail Stop 313(c)
Randolph Building
Alexandria, VA 22314

PETITION FOR WITHDRAWAL FROM ISSUE
PURSUANT TO 37 C.F.R. § 1.313(c)(2)

Sir:

Applicants respectfully petition for withdrawal of the above-identified patent application from issue.

A Notice of Allowance was mailed in this application on May 10, 2005. Applicant mailed the issue fee to the Patent Office on August 10, 2005.

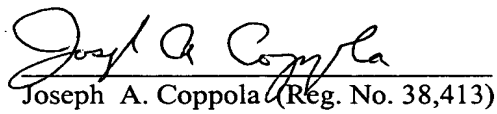
This petition to withdraw the application from issue is pursuant to 37 C.F.R. §1.313(c)(2) whereby Applicant requests continued examination in compliance with 37 C.F.R. §1.114 in order to permit consideration of an Information Disclosure Statement under 37 C.F.R. §1.97. A Request for Continued Examination and Information Disclosure Statement (and twenty (20) references) are being submitted herewith for filing.

08/24/2005 JADD01 00000052 110600 10766263
02 FC:1464 130.00 DA

The Office is authorized to charge the $130.00 petition fee under 37 C.F.R. §1.17(h), along with any other charges which may be associated with this paper or credit any overpayment to Kenyon & Kenyon Deposit Account 11-0600. A duplicate of this paper is enclosed for that purpose.

Respectfully submitted,

Dated: August 22, 2005

By: 
Joseph A. Coppola (Reg. No. 38,413)

KENYON & KENYON
One Broadway
New York, New York 10004
Telephone: (212) 425-7200
Facsimile: (212) 425-5288
CUSTOMER NO. 26646

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT		Docket Number: 12961/46102	
Application Number: 10/766,623	Filing Date: January 27, 2004	Examiner: Z. C. TUCKER	Art Unit: 1624
Invention Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		Inventor: Claus MEESE et al.	

Address to:
U.S. Patent and Trademark Office
Customer Window, Mail Stop 313(c)
Randolph Building
Alexandria, VA 22314

SIR:

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 35 U.S.C. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorneys for Applicant hereby brings the following references to the attention of the Examiner. These references are listed on the attached modified PTO Form No. 1449. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. The filing of this Information Disclosure Statement and the enclosed PTO 1449 shall not be construed as an admission that the information cited is prior art, or is considered to be material to patentability as defined in 37 C.F.R. §1.56(b).

3. A copy of each patent, publication or other information listed on the modified PTO 1449 (except U.S. patents) is enclosed, unless otherwise noted.

4. It is believed that no fees are due in connection with this Information Disclosure Statement. However, should any fees be due, the Commissioner is authorized to charge Deposit Account No. 11-0600 for such fees. A duplicate of this communication is enclosed for charging purposes.

Joseph A Coppola

Dated: August 22, 2005

By: Joseph A. Coppola (Reg. No. 38,413)
KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NUMBER 26646

NYO1 1033220 v1

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
INFORMATION DISCLOSURE STATEMENT		Docket Number: **12961/46102**	
Application Number **10/766,623**	Filing Date **January 27, 2004**	Examiner **Z. C. TUCKER**	Art Unit **1624**
Invention Title **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor **Claus MEESE et al.**	

Address to:
U.S. Patent and Trademark Office
Customer Window, Mail Stop 313(c)
Randolph Building
Alexandria, VA 22314

SIR:

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 35 U.S.C. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorneys for Applicant hereby brings the following references to the attention of the Examiner. These references are listed on the attached modified PTO Form No. 1449. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. The filing of this Information Disclosure Statement and the enclosed PTO 1449 shall not be construed as an admission that the information cited is prior art, or is considered to be material to patentability as defined in 37 C.F.R. §1.56(b).

3. A copy of each patent, publication or other information listed on the modified PTO 1449 (except U.S. patents) is enclosed, unless otherwise noted.

4. It is believed that no fees are due in connection with this Information Disclosure Statement. However, should any fees be due, the Commissioner is authorized to charge Deposit Account No. 11-0600 for such fees. A duplicate of this communication is enclosed for charging purposes.

Joseph A Coppola

Dated: August 22, 2005

By: Joseph A. Coppola (Reg. No. 38,413)
KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NUMBER 26646

NYO1 1033220 v1

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	ATTY. DOCKET NO. **12961/46102**	APPLICATION NO. **10/766,263**
Form PTO-1449	APPLICANT **Claus MEESE et al.**	
	FILING DATE **January 27, 2004**	GROUP **1624**

U. S. PATENT DOCUMENTS*

EXAMINER INITIAL	PATENT/PUBLICATION NUMBER	PATENT/PUBLICATION DATE	NAME	CLASS	SUBCLASS	FILING DATE*
	2,556,636	June 12, 1951	Nathan Sperber et al.			
	2,567,245	September 11, 1951	Nathan Sperber et al.			
	2,676,964	April 27, 1954	Nathan Sperber et al.			
	3,261,841	July 19, 1966	Bernard L. Zenitz			

*- copies of U.S. references are not enclosed

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	830,193	February 04, 1952	DE			X	
	685 696	January 07, 1953	GB				
	689 835	April 08, 1953	GB				
	690 274	April 15, 1953	GB				
	692 931	June 17, 1953	GB				
	1 169 944	November 05, 1969	GB				
	1 169 945	November 05, 1969	GB				
	WO 03/021271	March 13, 2003	PCT				

OTHER DOCUMENTS

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Abstracts from the 26th Annual Meeting of the International Incontinence Society, August 27-30, 1996, Gillberg et al., abstract 33, Neurology and Urodynamics 15:308-309
		Andersson & Hedlund, "Pharmacological perspective on the physiology of the lower urinay tract," 2002, Urology 60(Suppl. 5A):13-20
		Committee for Proprietary Medicinal Products, "The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products," CPMP/986/96, December 17, 1997
		Gardner & Altman, "Confidence intervals rather than P values: estimation rather than hypothesis testing," 1986, Br. Med. J. 292:746-750
		Kang et al., "Cardiac ion channel effects of Tolterodine," 2004, J. Pharmacol. Exper. Thera. 308:935-940
		Klosa, "Eine Neue Synthesemethode der Darstellung von Diarylalkylaminen," 1966, Journal für Praktische Chemie 4:312-334 (in German) with English translation

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Lipinsky et al., "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," 1997, Adv. Drug Deliv. Rev. 23:3-25
		Netzer et al., "Screening lead compounds for QT interval prolongation," 2001, Drug Discovery Today 6:78-84
		Nilvebrant et al., "Differences between binding affinities of some antimuscarinic drugs in the parotid gland an those in the urinary bladder and ileum," 1983, Acta Pharmacol. et Toxicol. 53 :304-313
		Pharmacology/Toxicology Review from Application Number 21-518, Center for Drug Evaluation and Research, pages 1-3
		Roy et al., "HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine," 1996, 94:817-823

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

[12961/39493]
Translation R Ferber x 6071

Translation of German Patent # 830 193

Inventors: Dr. Gustav Erhart, Dr. Walter Bestian

METHOD FOR PREPARING BASIC COMPOUNDS

It was found that compounds of the general formula

(see original 1)

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

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

(see original 2)

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

(see original 3).

Such halogenides are, for example,

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

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

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

Example 1

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

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

Example 2

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

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

Example 3

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

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

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

Example 4

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

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

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

Example 5

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

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

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

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

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

Example 6

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

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

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

What is claimed is:

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

(see original 4)

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

(see original 5),

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

(see original 6),

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

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

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
4. FEBRUAR 1952

DEUTSCHES PATENTAMT

PATENTSCHRIFT

Nr. 830 193

KLASSE 12p GRUPPE 5

p 21380 IV c/12p D

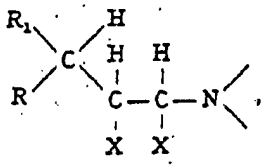
Dr. Gustav Ehrhart, Frankfurt/M.-Unterliederbach und
Dr. Walter Bestian, Frankfurt/M.-Zeilsheim
sind als Erfinder genannt worden

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

Verfahren zur Herstellung von basischen Verbindungen

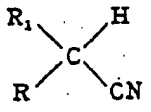
Patentiert im Gebiet der Bundesrepublik Deutschland vom 10. November 1948 an
Patenterteilung bekanntgemacht am 3. Januar 1952

Es wurde gefunden, daß Verbindungen der allgemeinen Formel

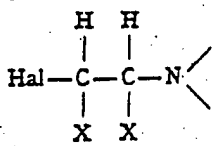


wobei R einen aromatischen und R_1 einen heterocyclischen Rest und X Wasserstoff oder Methyl bedeuten und N ein tertiär gebundenes Stickstoffatom ist, Spasmolytica darstellen, die sich insbesondere durch eine hervorragende Wirkung beim Histaminkrampf auszeichnen.

Zweckmäßig stellt man diese Verbindungen aus Nitrilen der allgemeinen Formel



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



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

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

Beispiel 1

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

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

Beispiel 2

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

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

Beispiel 3

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

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

Beispiel 4

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

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

Beispiel 5

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

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

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

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

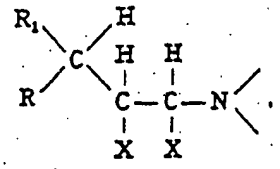
Beispiel 6

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

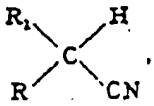
25 Gewichtsteile dieser Base werden mit 10 Gewichtsteilen Ätznatron, 100 Gewichtsteilen Äthanol (90%) 4 Stunden auf dem Dampfbad unter Rückfluß erwärmt. Bei der Aufarbeitung wird in quantitativer Ausbeute das 1-Phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropan vom $Kp_{0,1} = 136$ bis 139° erhalten.

PATENTANSPRUCH:

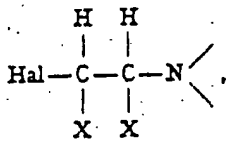
Verfahren zur Herstellung von basischen Verbindungen der allgemeinen Formel



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



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



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

© 2996 1.52

ODWS 24.7.03

AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General dated the eleventh day of October, 1957, under Section 33, of the Patents Act, 1949.

PATENT SPECIFICATION

GB 685,696

Date of Application and filing Complete Specification: Oct. 13, 1949.

No. 26316/49.

Application made in United States of America on Nov. 23, 1948.

Complete Specification Published: Jan. 7, 1953.

Index at acceptance:—Class 2(iii), B4a(2:4), B4(d:e), C1a(1:10), C1b(1:2), C1e4k(3:4:6:8), C1e5k(4:6:8), C1e6k(4:6:8), C1f2a(2:3), C1f2c(4:5:6), C1f2d(1:2:3), C2a(3:5:14), C2b3 (a4:b:f), C2b3g(1:7), C2b(4:9), C(2r17:3a:12), C3a13a3(a4:b3:f3), C3a13c(1c:2c:3c:6c:9), C3a13c10(f:h), C3a14a(3d:5:8d).

COMPLETE SPECIFICATION

Process for the Manufacture of Anti-Histaminic Compounds

We, SCHERING CORPORATION, having a place of business at 2, Broad Street, Bloomfield, County of Essex, State of New Jersey, United States of America, a corporation organized under the laws of the State of New Jersey, United States of America, (Assignee of NATHAN SPERBER, residing in Bronx, County of Bronx, State of New York, United States of America, and DOMENICK PAPA, residing in Brooklyn, County of Kings, State of New York, United States of America, both Citizens of the United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to new substances of interesting and important physiological properties and a process for their manufacture. More specifically, the invention relates to the preparation of compounds having pronounced antihistaminic activity.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

In specifications Nos. 307,304 and 646,198 (both as open to public inspection under Section 91 of the Patents Acts 1907—1946) general methods are described for the conversion of ketones of the formula:

$$R^3.CO.X.NR^1R^2$$

by Grignard reaction into carbinols:

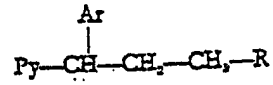
$$\begin{matrix} R_3 \\ R^4 \end{matrix}\!>\!C(OH).X.NR^1R^2$$

and in Specification No. 646,198 for the subsequent replacement of the hydroxyl group by hydrogen, R^1, R^2, R^3 and R^4 being monovalent organic radicals (NR^1R^2 may be a nitrogen ring residue) and X being a divalent linking group. The products are stated to have good musculotropic antispasmodic activity accompanied by low neurotropic antispasmodic activity. In Specification No. 646,198 as open to public inspection under Section 91 *N*-(3-phenyl - 3-*cyclo*hexylpropyl)-piperidinehydrochloride, obtained in this manner from N-piperidylpropiophenone and *cyclo*hexyl bromide, is said to have 12 times the musculotropic antispasmodic activity of papaverine.

We have now found that certain com-

pounds obtainable by similar general reactions possess to an outstanding degree antihistaminic and antianaphylactic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in more than 90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

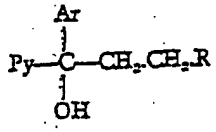
The selected compounds showing this advantage have the general formula



wherein Py stands for 2-pyridyl, Ar for phenyl or an alkyl-, alkoxy-, dialkylamino, chloro- or bromophenyl or for 2-thienyl, and R for a dialkylamino-, piperidino-, pyrrolidino-, or morpholino-group.

Throughout this specification the terms alkyl and alkoxy are used to denote groups having less than seven carbon atoms.

The compounds of the invention are produced by a process comprising the step of condensing a ketone $Ar.CO.CH_2.CH_2R$, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol

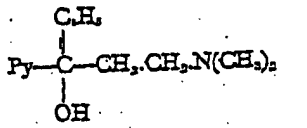


followed by replacement of the hydroxyl group by a hydrogen atom. The resulting bases may be converted into their salts by the usual methods.

Thus from β - dimethylaminopropiophenone (I)

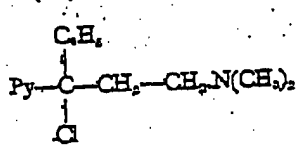
$$C_6H_5.CO.CH_2CH_2.N(CH_3)_2 \qquad (I)$$

there is obtained 1-(2'-pyridyl)-1-Phenyl-3-dimethylaminopropanol-1 (II):



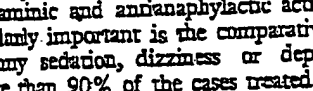
(II)

The carbinol (II) may be reacted with thionyl chloride to form the chloro-compound (III):



(III)

which on reduction with zinc dust and acetic acid gives in good yield the desired 1-phenyl-1-(2'-pyridyl)-3-dimethylaminopropane (IV)



(IV)

By a similar series of reactions compounds in which the phenyl group carries alkyl, alkoxyl, dialkylamino, chlorine or bromine substituents may be prepared. For the *p*-chloro-compound, for example the starting material is the ketone

p-$Cl.C_6H_4.CO.CH_2.CH_2.N(CH_3)_2$,

obtained by the Mannich reaction from *p*-chloroacetophenone, dimethylamine and formaldehyde.

By using diethylamine, piperidine, pyrrolidine or morpholine in place of dimethylamine the corresponding diethylamino-, piperidino-, pyrrolidino- or morpholino- ketone may be prepared.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2-pyridyl) - N,N - dimethypropylamine of Example I are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrogen chloride into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions comprise non-toxic salts.

EXAMPLE I.

1-Phenyl-1-(2'-pyridyl) - 3 - dimethylaminopropane.

The intermediate carbinol, phenyl - (2'-

pyridyl)-β-dimethylaminoethylcarbinol (II), is prepared as follows:

β-Dimethylaminopropiophenone hydrochloride (0.1 mole) is dissolved in 50 cc. of water and cooled in an ice-bath. The free base is liberated with ice and 10% sodium carbonate solution, and the oil is taken up in ether. The ether layer is washed with water and dried over anhydrous potassium carbonate. Upon removal of the ether, the free base is obtained.

A solution of 0.2 moles of 2-pyridyllithium in 250 ml. of ether is prepared and after cooling to −40° C., a solution of 18 g. of β-dimethylaminopropiophenone in 50 cc. of ether is added dropwise with stirring over a period of ½ hour. Upon completion of the reaction, the temperature is allowed to rise to −15° C. and the reaction mixture is stirred at this temperature for one hour. The contents of the flasks are decomposed with ice and hydrochloric acid and then made basic with gaseous ammonia. The resulting oil is taken up in ether, the ether evaporated and the residue distilled. The carbinol is a viscous, yellow syrup, boiling at 176—180° C./2 mm.

The carbinol (II) is converted to the propylamine as follows:

Phenyl-(2¹-pyridyl) - β - dimethylaminoethyl carbinol (II) (0.1 mole) is dissolved in 250 cc. of dry benzene and thionyl chloride (0.15 mole) added, keeping the temperature between 0 and 10° C. The reaction is allowed to come to room temperature, stirred for an additional ½ hour, and then made basic with a dilute solution of sodium hydroxide. The benzene layer is separated, dried and concentrated *in vacuo* leaving a viscous, purple oil. The crude phenyl-(2¹-pyridyl)-β-dimethylaminoethyl-methylchloride is dissolved in 200 cc. of glacial acetic acid and zinc dust (0.3 mole) added. The reaction mixture is stirred and heated on the steam bath for 6 hours, the zinc salts filtered and the filtrate concentrated *in vacuo*. The thick syrup is made alkaline with dilute sodium hydroxide and the oil which separates is extracted with ether. The ether layer is dried, concentrated and the residue distilled.

EXAMPLE II.

1(*p*-Methoxyphenyl)-1-(2¹-pyridyl)-3-dimethylaminopropane.

This compound is prepared by the procedure described in Example I using *p*-methoxyacetophenone in a Mannich condensation with formaldehyde and dimethylamine hydrochloride to prepare β-dimethylamino-*p*-methoxypropiophenone. The latter is then carried through the series of reactions described in Example I. The substituted propylamine is a pale yellow, viscous liquid; b.p. 172—175° C./1.5 mm.

EXAMPLE III.

1(*p*-Chlorophenyl)-1-(2¹-pyridyl)-3-dimethylaminopropane.

Using *p*-chlorophenylacetophenone in the Mannich reaction followed by the 2-pyridyllithium reaction and the series of reactions described in Example I the corresponding propylamine is prepared; b.p. 139—141° C./1.0 mm.

EXAMPLE IV.

1-(Phenyl)-1-(2¹-pyridyl)-3-diethylaminopropane.

By substituting β-diethylaminopropiophenone hydrochloride for the dimethylamino compound in Example I there is obtained the compound of this example; b.p. 156—157° C./2.0 mm.

EXAMPLE V.

1-(Phenyl)-1-(2¹-pyridyl)-3-N - piperidinopropane.

By substituting piperidine hydrochloride for dimethylamine hydrochloride in Example I, the piperidino compound is obtained as a viscous yellow liquid boiling at 176—177° C/3.5 mm.

EXAMPLE VI.

1-Phenyl-1-(2¹-pyridyl)-3-(N-pyrrolidyl)-propane.

The β-(1-pyrrolidyl)propiophenone is obtained by the Mannich condensation of acetophenone with formaldehyde and pyrrolidine. The free base is liberated from the hydrochloride and then is reacted with 2-pyridyllithium, followed by further reactions in accordance with the procedure of Example I. The pyrrolidylpropane is obtained as a pale yellow oil boiling at 164—166° C./2—3 mm.

EXAMPLE VII.

1-(*p*-Chlorophenyl)-1-(2¹-pyridyl)-3-(N-pyrrolidyl)propane.

This compound is obtained exactly as described for the unsubstituted compound of the above example using *p*-chloroacetophenone in place of acetophenone. The halogenated compound of this example is a yellowish liquid boiling at 175—177° C./1—2 mm.

The following are other typical amines prepared by the methods of the invention:

1-(2¹-Thienyl)-1-(2¹¹-pyridyl)-3 - dimethylaminopropane, b.p. 154° C./2 mm.

1-(*p*-Methylphenyl)-1-(2¹-pyridyl) - 3 - dimethylaminopropane, b.p. 137—140° C./0.5 mm.

1-(4¹ - Dimethylaminophenyl) - 1 - (2¹¹-pyridyl)-3-dimethylaminopropane, b.p. 183—185° C./1.5 mm.

1-(2¹,3¹-Dimethoxyphenyl)-1 - (2¹¹-pyridyl)-3-dimethylaminopropane, b.p. 195—200° C./1—2 mm.

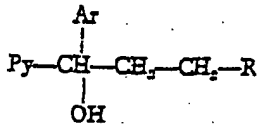
1-(*p*-Isopropylphenyl)-1-(2¹ - pyridyl) - 3-dimethylaminopropane, b.p. 147—152° C/1.0 mm.

What we claim is:—

1. The step in the production of pyridyl aliphatic amines and their salts which consists in reacting a ketone of formula

$$Ar.CO.CH_2.CH_2.R$$

wherein Ar stands for phenyl or for an alkyl-, alkoxy-, dialkylamino-, chloro- or bromophenyl and R stands for a dialkylamino-, piperidino-, pyrrolidino- or morpholino-group, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol



wherein Py stands for 2-pyridyl followed by replacement of the hydroxyl group in the resulting carbinol by hydrogen to give the compound.

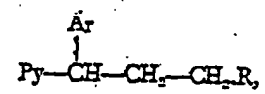
and conversion of the product, if desired, into its salts.

2. The step in the production of pyridyl-aliphatic amines and their salts as claimed in Claim 1 comprising the conversion of the carbinol into the corresponding halide, e.g. by the action of thionyl chloride and replacement of the halogen by hydrogen, e.g. by reduction with zinc dust and acetic acid, to give a compound of formula

and conversion of this product if desired, into its salts.

3. The steps as claimed in either of the preceding claims in which Ar stands for phenyl or p-chlorophenyl and R for dimethylamino or N-pyrrolidyl.

4. Process for the production of saturated compounds of the formula



substantially as described with reference to each of the foregoing Examples.

5. 3-(2'-Pyridyl)-3-arylpropylamines, whenever produced by the process claimed in any of the preceding claims.

6. Salts of 3-(2'-pyridyl)-3-aryl-propylamines whenever produced by the process claimed in any of Claims 1—3.

Dated this 13th day of October, 1949.

URQUHART-DYKES & LORD,
Maxwell House, 11, Arundel Street, Strand,
London, W.C.2, and
12, South Parade, Leeds 1,
Chartered Patent Agents.

Reference has been directed in pursuance of Section 9, sub-section (1) of the Patents Act, 1949 to Patent No. 689,234.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1957.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

GB 689,835

Date of Application and filing Complete Specification: Oct. 23, 1950.

No. 27281/49.

Application made in Germany on Sept. 5, 1949.

Complete Specification Published: April 8, 1953.

Index at acceptance:—Class 2(iii), B4a(2:4), B4e, C2a(3:5), C2r17.

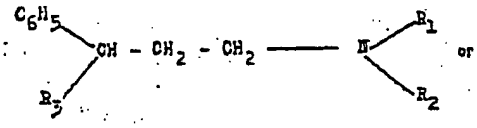
COMPLETE SPECIFICATION

Manufacture of Para-Aminosalicylates

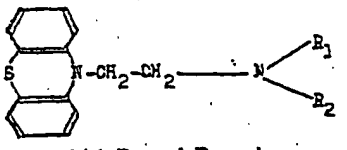
We, MICHAEL ERLENBACH and ADOLF SIEGLITZ, both German citizens, of Georg Voigtsstrasse 12, Frankfurt, Main, Germany, and Orienstrasse, Bad Soden, Taunus, Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The usual anti-histaminic substances are generally applied for therapeutic purposes in the form of salts of the corresponding bases with inorganic acids, the potency of the salt corresponding to that of the base diminished in proportion to the weight of the acid combined with the base. (Compare "Die Pharmazie," 1947, page 495; "Chemisches Zentralblatt," Verlag Chemie, 1947, Vol. I, pages 446 *et seq.*).

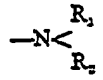
The present invention is based on the observation that the salts of anti-histaminic bases of the general formula



or



in which R_1 and R_2 each represents a methyl group or the grouping



represents a pyrrolidino group, and R_3 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid are distinguished by a surprisingly high anti-histaminic action. This action considerably exceeds that of the anti-histaminic base and the known salts thereof.

Although para-aminosalicylic acid itself exhibits a certain anti-histaminic effect, this does not suffice to explain the enhanced action of the salts, which is due to a synergistic action.

The salts of anti-histaminic bases with para-aminosalicylic acid are made in accordance with this invention by reacting equimolecular proportions of para-aminosalicylic acid with an anti-histaminic base, or by the double decomposition of an alkali salt or alkaline earth metal salt of para-aminosalicylic acid with a salt of an anti-histaminic base with an inorganic acid.

As examples of salts of anti-histaminic bases in accordance with the invention there may be mentioned especially 1-phenyl-1-pyridyl-(2¹)-3-dimethylaminopropane para-aminosalicylate, 1-phenyl-1-pyridyl-(2¹)-3-N-pyrrolidinopropane para-aminosalicylate, 1-phenyl-1-thiazolyl-(2¹)-3-N-pyrrolidinopropane para-aminosalicylate and 10-dimethylaminoethyl-phenthiazine para-aminosalicylate.

The following examples illustrate the invention, the parts being by weight unless otherwise stated, and the relationship of parts by weight to parts by volume being the same as that of the kilogram to the litre:

EXAMPLE 1.

1-PHENYL-1-PYRIDYL-(2¹)-3-DIMETHYLAMINOPROPANE PARA-AMINOSALICYLATE.

Equivalent quantities of 1-phenyl-1-pyridyl-(2¹)-3'-dimethyl-aminopropane and para-aminosalicylic acid are separately dissolved in ethyl acetate, and the two solutions are mixed together. The salt named above very soon separates in a practically quantitative yield. It melts at temperatures of 144—145° C. with decomposition, and is twice as potent as the corresponding phosphate.

EXAMPLE 2.

1-PHENYL-1-PYRIDYL-(2¹)-3-N-PYRROLIDINOPROPANE PARA-AMINOSALICYLATE.

5.32 parts of 1-phenyl-1-pyridyl-(2¹)-3-N-

[Price 2/8]

pyrrolidino-propane are dissolved in 40 parts by volume of acetone, and 6.12 parts of para-aminosalicylic acid are dissolved in 30 parts by volume of acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates which melt at 171—172° C. with decomposition. The yield is nearly quantitative. The para-amino-salicylate is soluble in water and about twice as potent as the corresponding phosphate.

EXAMPLE 3.
1-PHENYL-1-THIAZOLYL-(2')-3-N-PYRROLIDINOPROPANE PARA-AMINOSALICYLATE.

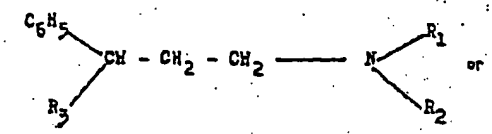
Equivalent quantities of para-aminosalicylic acid and 1-phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropane are separately dissolved in acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates melting at 161—162° C. with decomposition. The yield is practically quantitative. The product is soluble in water and twice as potent as the corresponding phosphate.

EXAMPLE 4.
10-DIMETHYLAMINOETHYL-PHENTHIAZINE PARA-AMINOSALICYLATE.

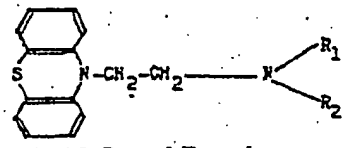
10 parts of 10-dimethylaminoethyl-phenthiazine hydrochloride are dissolved, while gently heating, in 120 parts of water, and the solution so obtained is mixed with a solution of 7 parts of sodium para-amino-salicylate in 50 parts by volume of water. The oily solution, which separates, rapidly becomes solid on rubbing. 13.3 parts of the para-aminosalicylate are obtained as a colourless salt which is sparingly soluble in water and readily soluble in hot acetone, in hot methyl alcohol and in ethyl acetate. It decomposes at 159—160° C. and is twice as potent as the hydrochloride of 10-dimethyl-aminoethyl-phenthiazine.

What we claim is:—

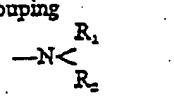
1. A salt of an anti-histaminic base of the general formula



or



in which R_1 and R_2 each represent a methyl group or the grouping



represents a pyrrolidino group, and R_3 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid.

2. 1-Phenyl-1-pyridyl-(2')-3-dimethylamino-propane para-aminosalicylate.

3. 1-Phenyl-1-pyridyl-(2')-3-N-pyrrolidino-propane para-aminosalicylate.

4. 1-Phenyl-1-thiazolyl-(2')-3-N-pyrrolidinopropane para-aminosalicylate.

5. 10-Dimethylaminoethyl-phenthiazine para-aminosalicylate.

6. A process for the manufacture of a salt of an anti-histaminic base claimed in any one of claims 1—5, wherein para-aminosalicylic acid and the anti-histaminic base are reacted together in equimolecular proportions or an alkali salt or an alkaline earth metal salt of para-aminosalicylic acid is reacted with a salt of the anti-histaminic base with an inorganic acid.

7. A process for the manufacture of a salt of an anti-histaminic base conducted substantially as described in any one of Examples 1—4 herein.

ABEL & IMRAY,
Agents for the Applicants,
Quality House, Quality Court, Chancery Lane, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

GB 690,274

Date of Application and filing Complete Specification: Oct. 18, 1948.

No. 27020/48.

Application made in United States of America on Oct. 28, 1947.

Complete Specification Published: April 15, 1953.

Index at acceptance:—Classes 2(iii), B4a(1: 2), B4(c: d), C1a10, C1b(1: 2), C2a[illegible], C2b3(a4: b: d: f), C2b3g(1: 8), C2b(18: 20), C2r[illegible] and 81(i), B11b1(a: c: g: i), B11b2(a: c: g: i).

COMPLETE SPECIFICATION

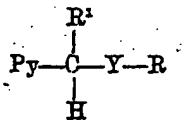
Antihistaminic Substances

We, SCHERING CORPORATION, a corporation of the State of New Jersey, of 2, Broad Street, Bloomfield, New Jersey, United States of America, (Assignees of NATHAN SPERBER, 1456, Minford Place, Bronx, New York, DOMENICK PAPA, 17th Avenue, Brooklyn, New York and ERWIN SCHWENK, 10, Crestmont Road, Montclair, New Jersey, United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed to be particularly described and ascertained in and by the following statement:—

The invention relates to the manufacture of new substances of interesting and important physiological properties and more particularly to the manufacture of pyridyl substituted alkanes which have been found to be highly effective against histamine-induced allergic reactions.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance, they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

It has been generally considered that only those substances which are derivatives of ethanolamine and ethylenediamine show pronounced anti-histaminic and antianaphylactic activity. It has now been found that pyridyl aliphatic amines of the general formula

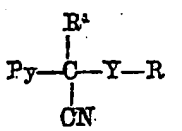


wherein Y stands for an alkylene group having 2 or 3 carbon atoms, Py is a pyridine ring which may be substituted by a halogen, alkoxy or lower alkyl group, R represents a dialkylamino, piperidino, morpholino, or iminazolinyl group, and R^1 represents an alkyl, aryl, aralkyl *cyclo*alkyl or heterocyclic group or an alkyl, alkoxy, dialkylamino, chloro or bromo derivative of such groups, and the salts thereof with inorganic and organic acids, possess to an extremely high degree antihistaminic and antianaphylactic activity.

Throughout this Specification and claims it is to be understood that by the terms "alkyl," "alkoxy" (or "alkoxyl") and "dialkylamino" we mean groups in which the alkyl is a lower alkyl, i.e. contains not more than four carbon atoms.

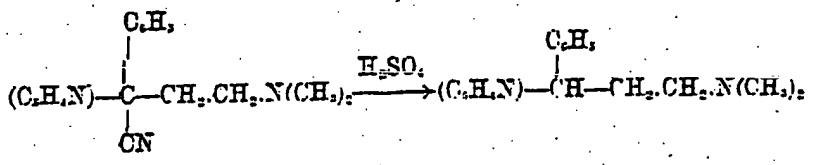
Clinical studies with representative members of the compounds of this invention have demonstrated extremely favorable antihistaminic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in 85—90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

The method of the invention comprises the hydrolysis and decarboxylation of the nitriles of the general formula



in which Py, Y, R and R' have the significance above mentioned.

When the nitriles are treated with a strong acid, the nitriles are hydrolysed and decarboxylated to the compounds of the invention as illustrated by the following equation:



Suitable nitriles for use in making the compounds of the invention may be made (as described in co-pending Application No. 25947/48 (Serial No. 666,778) by:

(a) condensing a pyridyl or alkylpyridyl halide with an alkane or substituted alkane nitrile to form a pyridyl alkane nitrile and thereafter condensing the latter product with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide;

(b) condensing an alkane, or substituted alkane, nitrile with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide and condensing the product with a pyridyl or alkylpyridyl halide; or

(c) condensing in one operation an alkane, or substituted alkane nitrile and a pyridyl or alkylpyridyl halide with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide.

The condensations are advantageously effected by heating the reactants in an organic solvent, such as toluene or xylene or in liquid ammonia, in the presence of condensation catalysts, such as alkali metals, alkali metal amides, alkali metal alkoxides, or alkali metal organo compounds, for example, butyllithium or triphenylmethyl sodium.

The following specific example is illustrative of the method and products of the invention.

EXAMPLE.

3-PHENYL-3-(2'-PYRIDYL)-N,N-DIMETHYLPROPYLAMINE.

To 400 g. of α-phenyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile there is added 2,000 g. of 80% sulfuric acid. The mixture is heated with stirring at 140—150° C. for 24 hours. After dilution with ice and water, the aqueous sulfuric acid solution is made alkaline with ammonia gas. The oil which separates out is extracted with ether. The extract is dried, and, after removing the ether, the residue is distilled giving the 3-phenyl-3-(2'-pyridyl)-N,N-dimethylpropylamine, b.p. 139—142° C./1—2 mm.

In addition to the hydrolysis and decarboxylation of the nitriles with 80% sulfuric acid, the conversion may be effected in other ways. For example:

(a) One part of the nitrile and ten parts of 48% hydrobromic acid are refluxed for a period of 50—60 hours. The aqueous hydrobromic acid is removed *in vacuo*. The residue is made alkaline with gaseous ammonia and the oil which separates is extracted with ether. The ether residue is treated with a saturated alcoholic solution of picric acid heated to boiling and filtered. The insoluble picrate is washed with boiling alcohol. This purification process removes any starting material which, unlike the amine, forms an alcohol soluble picrate. The insoluble picrate is then decomposed with dilute sodium hydroxide, the amine is isolated by extraction with ether and purified by distillation.

(b) To one part of the nitrile there is added five parts of 80% sulfuric acid and one part of 48% hydrobromic acid. The mixture is heated at a temperature of 130—140° C. for about 30—40 hours and the reaction mixture worked up as in method (a).

(c) One part of the nitrile is refluxed with concentrated hydrochloric acid for about 60 hours. The amine thus formed is isolated and purified as described under method (a).

The following compounds having substantial antihistaminic activity may be made from the corresponding nitriles by the methods of the Example:

3-Phenyl-3-(2'-pyridyl)-N,N-diethylpropylamine, a yellow oil boiling at 156° C./1 mm., from α-phenyl-α-(β-diethylaminoethyl)-2-pyridylacetonitrile.

4-Phenyl-3-(2'-pyridyl)-N,N-dimethylbutylamine, boiling at about 135° C./0.5 mm., from α-benzyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(2'-Thienyl)-3-(2'-pyridyl)-N,N-dimethylpropylamine, a pale yellow oil boiling at 154° C./2 mm., from α-(2'-thienyl)-α-(β'-dimethylaminoethyl)-2-pyridylacetonitrile.

4-(2¹¹-Thienyl)-3-(2¹ - pyridyl) - N,N-dimethylbutylamine, boiling at 130—133° C./0.1 mm., from α-(2¹-thienylmethyl)-α - (β¹ - dimethylaminoethyl) - 2-pyridylacetonitrile.

3 - (*p* - Methylphenyl) - 3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 130—135° C./0.5 mm., from α-(*p*-methylphenyl) - α - (β¹ - dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Methoxyphenyl)-3 - (2¹ - pyridyl)-N,N - dimethylpropylamine, boiling at about 137—142° C./0.5 mm., from α-(*p*-Methoxyphenyl)-α - (β¹ - dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Isopropylphenyl)-3-(2¹ - pyridyl)-N,N-dimethylpropylamine, boiling at 144—147° C./1mm., from α-(*p*-isopropylphenyl)-α-(β¹ - dimethylaminoethyl) - 2-pyridylacetonitrile.

3-Phenyl- 3 - (6¹ - methyl - 2¹-pyridyl)-N,N-dimethyl-propylamine, boiling at 171—175° C./1 mm., from α-(β¹-dimethylaminoethyl) - α - (6 - methyl - 2-pyridyl)-phenylacetonitrile.

3-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 147—152° C./0.5 mm., from α-(*p*-bromophenyl)-α - (β¹ - dimethylaminoethyl) - 2-pyridylacetonitrile.

4-Phenyl-4-(2¹-pyridyl) - 2 - (dimethylamino)-butane, from α-phenyl - α - (2-pyridyl)-γ-(dimethylamino)-valeronitrile.

4-Phenyl-4-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-phenyl-α-(2-pyridyl)-γ-(dimethylaminomethyl)-butyronitrile.

3-Phenyl-2-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-benzyl-α-(2-pyridyl)-β-dimethylaminopropionitrile.

3-Cyclohexyl-3-(2¹-pyridyl) - N,N - dimethylpropylamine, from α-cyclohexyl-α-(β¹ - dimethylaminoethyl) - 2 - pyridylacetonitrile.

3-Cyclohexyl-4-(2¹-pyridyl) - N,N - dimethylbutylamine, from β-cyclohexyl-α-(β-dimethylaminoethyl)-α - (2 - pyridyl)-propionitrile.

3-(5¹¹ - Bromo - 2¹¹ - thienyl)-3 - (2¹-pyridyl)-N,N-dimethylpropylamine, from α-(5-bromo-2 - thienyl) - α-(β¹ - dimethylaminoethyl)-2-pyridylacetonitrile.

4-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-(*p*-bromobenzyl)-α - (β¹ - dimethylaminoethyl) - 2-pyridylacetonitrile.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2¹ - pyridyl) - N,N - dimethyl-propylamine of the Example are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrochloric acid into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N -dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

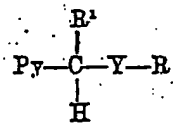
4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms, such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions preferably comprise non-toxic salts in admixture with sodium carbonate and boric acid and are sterilized before use.

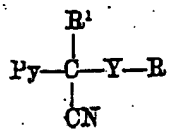
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the manufacture of antihistaminic substances of the general formula:



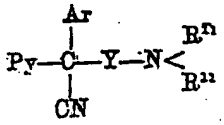
where Py represents a pyridine residue which may carry halogen, alkyl or alkoxy as substituents, Y stands for an alkylene group having 2 or 3 carbon atoms, R represents a dialkylamino-, piperidino-, morpholino- or iminazolino-group and R^1 stands for alkyl, aryl, aralkyl, cycloalkyl or a heterocyclic residue, which may carry as substituents alkyl, alkoxyl, dialkylamino, chlorine or bromine, and of salts of such compounds, said process comprising the hydrolysis and decarboxylation of a nitrile having

the formula:—



by reaction with a strong acid, e.g. with 80% sulphuric acid.

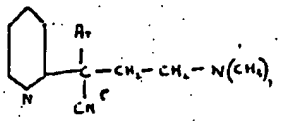
2. A process as claimed in Claim 1 in which the nitrile has the formula



where Py and Y have the same significance as in Claim 1, Ar stands for an aryl group, and either R^{11} is an alkyl group or $N<^{R^{11}}_{R^{11}}$ stands for a piperidine residue.

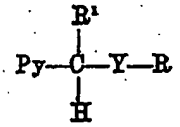
3. A process as claimed in Claim 2 in which Py is 2-pyridyl, Ar is phenyl or *p*-chlorophenyl, and R^{11} is methyl.

4. A process for the manufacture of 3-phenyl- and 3-*p*-chlorophenyl - 3 - (2'-pyridyl) - N,N - dimethylpropylamines, and of salts of these, by hydrolysis and decarboxylation of the nitriles of formula



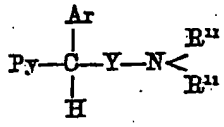
(where Ar stands for phenyl or *p*-chlorophenyl) by reaction with a strong acid, e.g. with 80% sulphuric acid, the base produced being converted into salts as desired.

5. Compounds of the formula:



where Py, R and R^1 have the same significance as in Claim 1 and salts thereof whenever produced by the process of any of the preceding claims or by an obvious chemical equivalent of such process.

6. Compounds of the formula:



in which Py and Y have the same significance as in Claim 1, Ar stands for phenyl, a chlorophenyl, an alkylphenyl or an alkoxyphenyl, and R^{11} stands for alkyl and salts thereof whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

7. Compounds as claimed in Claim 6 in which Ar is phenyl or *p*-chlorophenyl, Y is $.CH_2.CH_2.$ and R^{11} is methyl, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

8. Compounds as claimed in Claim 6 in which Py is 2-pyridyl. Y is $.CH_2.CH_2.$. and $N<^{R^{11}}_{R^{11}}$ stands for a dialkylamino group or for the N-piperidino radical, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

Dated this 18th day of October, 1948.

URQUHART-DYKES & LORD,
Maxwell House, 11, Arundel Street,
Strand, London W.C.2, and
12, South Parade, Leeds, 1,
Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

DWS 24.7.03

PATENT SPECIFICATION

GB 692,931

Date of Application and filing Complete Specification: March 23, 1950.
No. 8128/49.
Application made in Germany on Nov. 9, 1948.
Application made in Germany on Dec. 2, 1948.
Application made in Germany on Dec. 24, 1948.
Complete Specification Published: June 17, 1953.

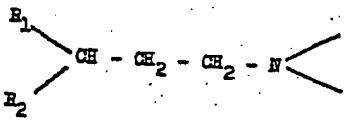
Index at acceptance:—Classes 2(iii), B4a(1: 2: 3: 4), B4(d: e), C2a(3: 14), C2b3(a4: b: g8), C2(b18: r17: s16: t16).

COMPLETE SPECIFICATION

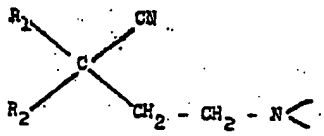
Basically Substituted Propane Compounds and the Manufacture thereof

We, MICHAEL EHLENBACH and ADOLF SIEGLITZ, both German citizens, and of Georg Voigtstrasse 12, Frankfurt (Main), Germany, and Oranienstrasse, Bad Soden (Taunus), Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention consists in a process for the manufacture of the basic compounds of the general formula



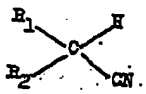
in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula



in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

As the alkali hydroxide there may be used potassium hydroxide.

The nitriles used as starting materials in the present process may be obtained by reacting a nitrile of the general formula

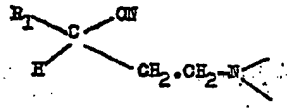


in which R_1 and R_2 have the meanings given above, with a basically substituted alkyl halide of the general formula

$$Hal—CH_2—CH_2—N<$$

in which N< has the meaning given above, in the presence of sodamide or another agent capable of eliminating hydrogen halide. Halides of this kind are, for instance, N-β-chlorethyl-dimethylamine, N-β-chlorethyl-diethylamine, 1-chloro-2-dimethylamino-propane, N-β-chlorethyl-piperidine, N-β-chlorethyl-pyrrolidine and N-β-chlorethyl-morpholine.

Alternatively the nitriles may be obtained by reacting a nitrile of the general formula

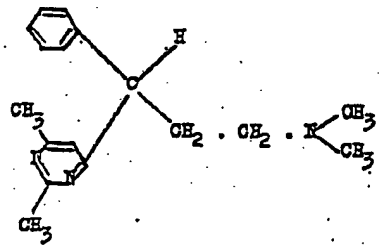


in which R_1 and N< have the meanings given above, with a halogen-substituted heterocyclic compound in the presence of sodamide or another agent capable of eliminating hydrogen halide. As halogen-substituted heterocyclic compounds there may be used, for example 2-chloropyridine, 2-chlorothiazole, 2:6-dimethyl-4-chloropyrimidine, 2-chlorobenzthiazole or 4-chloroquinoline.

The products of the present invention are more or less viscous oils, which can be converted into salts which dissolve

[Price 2/8]

well in water, and among which salts the phosphates have been found to be especially useful. The products exhibit excellent antispasmodic properties which are especially pronounced in the case of histamine spasms. There come into consideration more especially 1-phenyl-1-thiazole-(2')-3-dimethyl - aminopropane and 1 - phenyl - 1 - [2':6' - dimethyl-pyrimidyl-(4')]-3-dimethylamino-propane of the formula



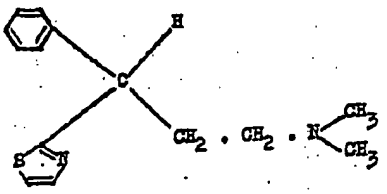
which boils at 122—126° C. under a pressure of 0.1 mm.

The following Examples illustrate the invention, the parts being by weight:—

EXAMPLE 1.

94 parts of α-phenyl-γ-dimethylamino-butyric acid nitrile are heated for 1 hour at 80° C. together with 200 parts of toluene and 22 parts of sodamide. After cooling, 60 parts of 2-chlorothiazole are added, and the product of the reaction is heated for 2 hours at 110° C. After decomposing the reaction product with water and separating the organic solution, there is obtained by fractional distillation, after a small quantity of first runnings, α-phenyl-α-thiazolyl - (2) - γ - dimethyl-amino-butyric acid nitrile boiling at 150—153° C. under a pressure of 0.25 mm. in a very good yield.

By heating the product for 2 hours with an excess of an alcoholic solution of potassium hydroxide, 1 - phenyl - 1-thiazolyl-(2')-3-dimethylamino-propane of the formula

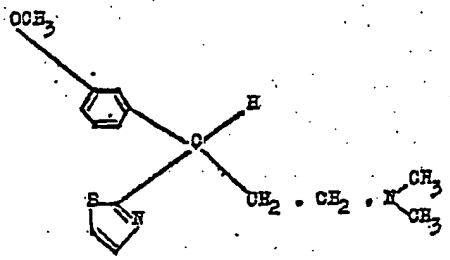


boiling at 136—138° C. under a pressure of 0.6 mm. is obtained in a very good yield. The phosphate containing two molecular proportions of water of crystallisation melts at 78—80° C.

EXAMPLE 2.

65.4 parts of α-(3-methoxyphenyl)-γ-dimethyl-amino-butyric acid nitrile (prepared from 3-methoxy benzyl cyanide, β - chlorethyl - dimethylamine and sodamide), 150 parts of toluene and 12.5 parts of sodamide are reacted with 36 parts of 2-chlorothiazole, and the product is heated for 1½ hours at about 110° C. The product is decomposed with water and subjected to a fractional distillation. α - (3 - Methoxy phenyl) - α - thiazolyl-(2)-γ-dimethylammino-butyric acid nitrile distils in good yield at a temperature of 155—160° C. under a pressure of 0.15 mm. in the form of a highly viscous yellow oil.

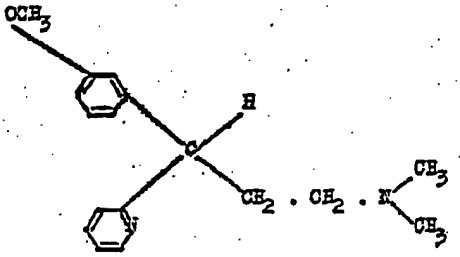
The nitrile group is then eliminated by treatment with an alcoholic solution of potassium hydroxide as described in Example 1 and there is obtained 1-(3'-methoxyphenyl) - 1 - thiazolyl - (2') - 3-dimethylaminopropane of the formula



boiling at 150—154° C. under a pressure of 0.5 mm.

EXAMPLE 3.

32.5 parts of α-(3-methoxyphenyl-γ-dimethylamino-butyric acid nitrile, 100 parts of toluene and 6 parts of sodamide are reacted with 17 parts of 2-chloropyridine. By fractional distillation of the reaction product α-(3-methoxyphenyl)-α-pyridyl-(2)-γ-dimethylamino-butyric acid nitrile is obtained in a good yield, in addition to unchanged starting material. The product so obtained is a viscous reddish oil boiling at 168—170° C. under a pressure of 0.3 mm., from which, by eliminating the nitrile group in the manner described in Example 1, there is readily obtained the corresponding propane of the formula

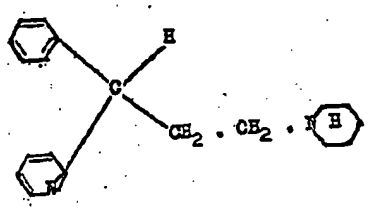


which boils at 155—160° C. under a pressure of 0.5 mm.

EXAMPLE 4.

13 parts of sodamide are introduced at 25—35° C. into a solution of 58.3 parts of phenyl - pyridyl-(2)-acetonitrile in 200 parts of benzene. The mixture is heated for a short time at 60—70° C. It is then cooled, and 48.5 parts of piperidino-ethyl chloride (boiling at 68—70° C. under a pressure of 12 mm.) are introduced dropwise. On heating to 50—60° C. the reaction sets in. Finally the reaction product is heated for 1 hour to 80° C., decomposed with water, and the benzene solution is separated. After a small amount of first runnings has distilled, α-phenyl-α-pyridyl-(2) - γ - (N-piperidino)-butyric acid nitrile distils at 185—190° C. under a pressure of 0.4 mm. in a yield of 90—95 per cent. in the form of a red viscous oil.

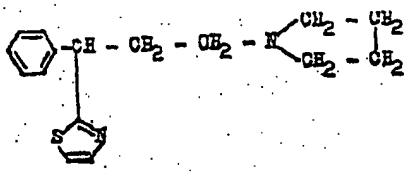
By treatment with an alcoholic solution of alkali 1-phenyl-1-pyridyl-(2')-3-piperidino-propane of the formula



is obtained in a very good yield in the form of a slightly coloured viscous oil boiling at 160—164° C. under a pressure of 0.25 mm.

EXAMPLE 5.

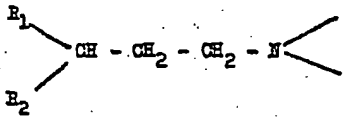
48 parts of α-phenyl-γ-N-pyrrolidino-butyric acid nitrile, boiling under a pressure of 0.1—0.2 mm. at 130—134° C., are heated for 30 minutes at 70—80° C. with 9.3 parts of sodamide in 200 parts of toluene, and, after cooling, gradually mixed with 27 parts of 2-chloro-thiazole at a temperature of 25—40° C. The mixture is heated for one hour at 90—95° C., mixed with 150 cc. of water, the toluene solution is separated and fractionally distilled. In addition to unchanged starting materials, α-phenyl-α-thiazolyl-(2)-γ-N-pyrrolidino-butyric acid nitrile is obtained as a viscous yellow oil boiling at 165—168° C. under a pressure of 0.15 mm. and melting at 83—85° C. 25 parts of this nitrile are boiled under reflux on the steam bath for 4 hours with 10 parts of caustic soda, 100 parts of ethyl alcohol and 10 parts of water. By working up in the usual manner 1-phenyl-1-thiazolyl-(2')-3 - N - pyrrolidino - propane of the formula



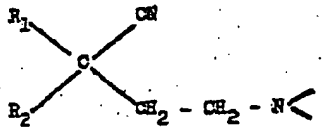
is obtained boiling at 136—139° C. under a pressure of 0.1 mm.

What we claim is:—

1. A process for the manufacture of the basic compounds of the general formula



in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula

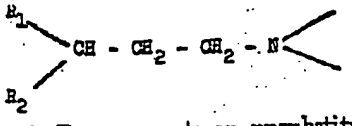


in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

2. A process as claimed in claim 1, wherein the alkali hydroxide is potassium hydroxide.

3. A process for the manufacture of the basic compound of any one of the Examples herein conducted substantially as described in that Example.

4. Basic compounds of the general formula

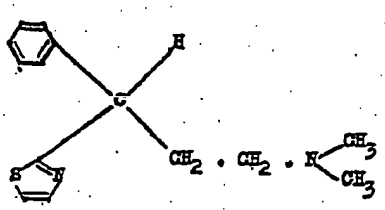


in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, when obtained by the process claimed in any one of claims 1—3.

5. Basic compounds as claimed in claim 4, wherein N< represents a dialkylamino group.

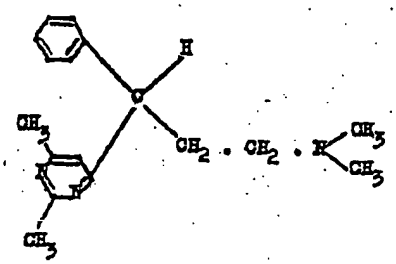
6. Basic compounds as claimed in claim 4, wherein N< represents a heterocyclic amino group.

7. 1 - Phenyl - 1 - thiazolyl-(2')-3-dimethylaminopropane of the formula



boiling at 136—138° C. under a pressure of 0.6 mm., when obtained by the process claimed in any one of claims 1—3.

8. 1 - Phenyl - 1 - [2':6' - dimethylpyrimidyl-(4')] - 3 - dimethylaminopropane of the formula



boiling at 122—126° C. under a pressure of 0.1 mm., when obtained by the process claimed in claim 1 or 2.

9. Any one of the basic compounds specified as end products of Examples 2—5 when obtained by the method substantially as described in that Example.

ABEL & IMRAY,
Agents for the Applicant,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2. from which copies may be obtained.

1,169,944

PATENT SPECIFICATION

NO DRAWINGS

1,169,944

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38195/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance:—C2 C(1H1A3, 1H1C2, 1Q2, 1Q3, 1Q6B1, 1Q7A, 1Q8A, 1Q8C, 1Q9C, 1Q9F2, 1Q11D, 1Q11J, 2A2, 2A5, 2A14, 2R17, 22Y, 220, 226, 227, 29Y, 29X, 30Y, 304, 32Y, 323, 36Y, 364, 650, 662, 682, 790, LF)

International Classification:—C 07 c 87/28, 93/14

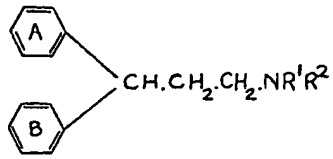
COMPLETE SPECIFICATION

Novel 3,3-Diphenylpropylamines and processes for the preparation thereof

We, ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate organised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new 3,3-diphenylpropylamine derivatives which have antidepressant activity.

According to the invention we provide alkane derivatives of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, and R^2 stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, and acid-addition salts thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R^1 and R^2 do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R^1 and R^2 do not both stand for the ethyl radical.

As a suitable value for R^2, or for R^1 when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl radical.

The substituent(s) which may be present in the phenyl radical A may, for example, be selected from fluorine and chlorine atoms, and the trifluoromethyl radical. The substituent(s) which is or are present in the phenyl radical (B) may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms, for example the methyl and methoxy radical.

Preferred compounds of the invention are those wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

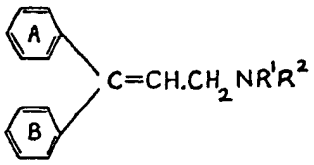
As specific alkane derivatives of the invention there may be mentioned, by way of example, N,N - dimethyl - 3, 3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl)-3-phenylpropylamine, N,N - dimethyl - 3,3 - bis-(4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - fluorophenyl)propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)-propylamine, N,N - dimethyl - 3,3 - bis - (3-trifluoromethylphenyl)propylamine and N,N -

[*Price 4s. 6d.*]

dimethyl - 3 - (3 - trifluoromethylphenyl)-3 - phenylpropylamine, and acid-addition salts thereof.

As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

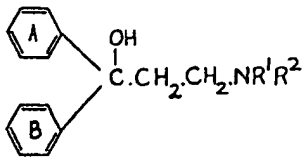
According to a further feature of the invention we provide a process for the manufacture of the alkane derivatives of the invention, which comprises reducing an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof.

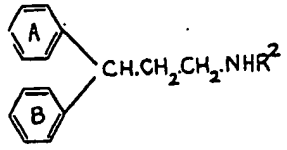
The reduction may be carried out, for example, by catalytic hydrogenation, for example by hydrogenation in the presence of a palladium-on-carbon catalyst. The hydrogenation may be carried out in an inert diluent or solvent, for example ethanol, and it may be carried out at ambient temperature or under the influence of heat, and at atmospheric or an elevated pressure. Alternatively, for example, the reduction may be carried out by the interaction of the alkene derivative with red phosphorus and hydriodic acid. In this case the alkene derivative may conveniently be formed *in situ* by interaction of the corresponding tertiary alcohol with red phosphorus and hydriodic acid.

The alkene derivatives used as starting materials in the above process (some of which are described and claimed in our co-pending Application No. 8165/66 (Serial No. 1134715) may be obtained by dehydrating the corresponding hydroxy compounds of the formula:

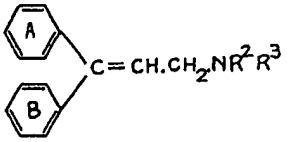


wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof, by the interaction thereof with hydrochloric acid in the presence of a diluent or solvent, for example acetic acid.

According to a further feature of the invention we provide a process for the manufacture of those of the alkane derivatives of the invention which are of the formula:—



wherein A, B and R^2 have the meanings stated above, and acid-addition salts thereof, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R^2 have the meanings stated above, and R^3 stands for a hydrogenolysable group, or an acid-addition salt thereof.

As a suitable value for R^3 there may be mentioned, for example, the benzyl radical. The hydrogenolysis may be carried out by catalytic hydrogenation using the reactants and conditions described above.

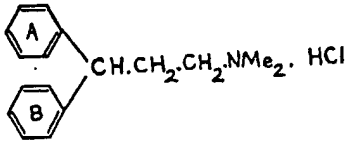
The starting materials in the last-named process may be obtained by the general dehydration process outlined above.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

5 Parts of N,N - dimethyl - 3,3 - bis - (4-fluorophenyl)prop- 2 -enylamine hydrochloride are dissolved in 20 parts of dry ethanol. 2.5 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated to a small volume. Dry ether is slowly added until crystallisation begins, and 500 parts of dry ether are then added. The mixture is filtered and the solid residue is washed with dry ether and then dried. The solid is crystallised from ethyl acetate containing a trace of ethanol, and there is thus obtained N,N-dimethyl-3,3 - bis - (4 - fluorophenyl)propylamine hydrochloride, m.p. 188—189°C.

In a similar manner, using the appropriate alkene derivative as starting material, the following compounds are obtained:—



A	B	m.p. (°C.)	Crystallisation solvent(s)
Ph	4—F—Ph	141—144	n-butyl acetate
Ph	4—Cl—Ph	154—157	ethyl acetate—trace of ethanol
Ph	3—F—Ph	166—168	"
Ph	2—Me—Ph	165—167	"
Ph	2—MeO—Ph	166—167	"
Ph	3—CF_3—Ph	145—148	ethyl acetate — petroleum ether (b.p. 60—80°C.)
4—Cl—Ph	4—Cl—Ph	193—196	n-butyl acetate
4—Cl—Ph	4—F—Ph	173—176	n-butyl acetate
3—F—Ph	3—F—Ph	178—180	ethyl acetate—trace of ethanol
3—CF_3—Ph	3—CF_3—Ph	158—160	ethyl acetate — petroleum ether (b.p. 60—80°C.)

The N,N - dimethyl - 3,3 - bis-(4-fluorophenyl)prop - 2 - enylamine hydrochloride used as starting material in the process described above may be obtained as follows:—

A mixture of 6 parts of N,N - dimethyl-3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine (m.p. 120°C.), 50 parts of acetic acid and 15 parts of 10N-hydrochloric acid is heated at 100°C. for 3 hours. The reaction mixture is evaporated to small volume and the residual oil is dissolved in water. The solution is washed with ether and is then made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and an ethereal solution of hydrogen chloride is then added to the extract until the precipitation of solid is complete. The precipitated solid is collected by filtration and is then crystallised from butyl acetate. There is thus obtained N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, m.p. 209°C.

The N, N - dimethyl - 3,3 - bis - (4-fluorophenyl) - 3 - hydroxypropylamine used as starting material can be obtained in conventional manner by the interaction of the appropriate Grignard reagent with the appropriate ketone.

The alkene derivatives used as starting materials for the preparation of the alkane derivatives listed in the above table may be obtained in similar manner to that described for N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)prop - 2 - enylamine hydrochloride.

EXAMPLE 2

6 Parts of N - benzyl - N - methyl-3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride are dissolved in 30 parts of dry ethanol. 3 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated. The residue is dissolved in 50 parts of water, and the solution is basified with ammonia. The base is extracted twice, each time with 100 parts of ether, and the combined ethereal extracts are dried with anhydrous magnesium sulphate. To the dry ethereal solution there is added an ethereal solution of oxalic acid until precipitation is complete. The mixture is filtered, and the solid residue is washed with ether and then dried on the filter. The solid is crystallised from ethanol, and there is thus obtained N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine oxalate, m.p. 187—190°C.

The N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride used as starting material may be obtained as follows:—

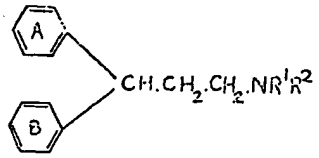
A mixture of 58.3 parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine, 465 parts of acetic acid and 117 parts of 10N-hydrochloric acid is heated under reflux for 0.5 hour. The mixture is evaporated to small volume and the residual oil is dissolved in water. The solution

is made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and is evaporated *in vacuo*. The residual oil is fractionally distilled at a pressure of 0.2mm. Hg. and the fraction having b.p. 172—178°C. is collected. There is thus obtained N - benzyl-N - methyl - 3,3 - bis - (4 - fluorophenyl)-prop - 2 - enylamine, which may be converted into the hydrochloride (m.p. 132°C.) by conventional means.

N - Benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine can be obtained in conventional manner by the interaction of ethyl 3 - (N - benzyl - N - methylamino)propionic acid and the appropriate Grignard reagent.

WHAT WE CLAIM IS:—

1. An alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, and R^2 stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R^1 and R^2 do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R^1 and R^2 do not both stand for the ethyl radical.

2. A compound as claimed in claim 1 wherein R^1 stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R^2 stands for an alkyl radical of not more than 6 carbon atoms, and the phenyl radical A optionally bears one or two substituents selected from fluorine and chlorine atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

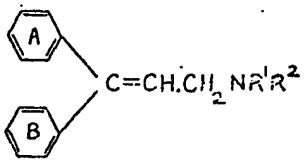
3. A compound as claimed in claim 1 wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

4. A compound as claimed in claim 3 wherein the halogen substituent(s) present in phenyl radical B, and optionally present in phenyl radical A, is or are selected from fluorine and chlorine atoms.

5. A compound selected from N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3,3 - bis - (4 - chlorophenyl)-propylamine, N,N - dimethyl - 3 - (4-chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3-fluorophenyl)-propylamine, N - methyl - 3,3 - bis - (4-fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

6. An acid-addition salt as claimed in any of claims 1 to 5 which is a hydrochloride, oxalate, citrate, maleate or tartrate.

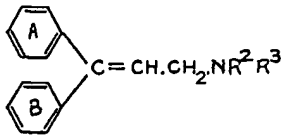
7. A process for the manufacture of a compound claimed in any of claims 1 to 6, which comprises reducing an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated in claim 1, or an acid-addition salt thereof.

8. A process as claimed in claim 7 in which the reduction is carried out by hydrogenation in the presence of a palladium-on-carbon catalyst.

9. A process for the manufacture of a compound claimed in claim 1 wherein R^1 stands for hydrogen, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R^2 have the meanings stated above, and R^3 stands for a hydro-

genolysable group, or an acid-addition salt thereof.

10. An alkane derivative, claimed in claim 1, substantially as described in either of the foregoing Examples.

11. A process for the manufacture of an alkane derivative, claimed in claim 7 or 9, substantially as described in either of the foregoing Examples.

B. F. DREW,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

1,169,945

PATENT SPECIFICATION

NO DRAWINGS

1,169,945

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38196/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance:—A5 B(38Y, 383, 43Y, 431, 58Y, 586, 64Y, 641)

International Classification:—A 61 k 27/00

COMPLETE SPECIFICATION

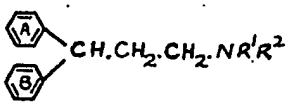
Pharmaceutical Compositions containing Diphenylalkylamine Derivatives

We, ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate oganised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pharmaceutical compositions having antidepressant activity.

Certain 3,3-diphenylpropylamine derivatives are known compounds, but it was not known heretofore that compounds of this type were useful as antidepressants. We have now made the unexpected discovery that compounds of this type have antidepressant activity, and therein lies the basis of this invention.

According to the invention we provide pharmaceutical compositions comprising at least one alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, R^2 stands for an alkyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

As a suitable value for R^2, or for R^1 when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl or ethyl radical.

The substituent(s) which may optionally be present in either or both or the phenyl radicals A and B may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkoxy and alkyl radicals of not more than 3 carbon atoms, for example the methoxy or methyl radical.

A preferred group of active ingredients consists of alkane derivatives of the above formula wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

As alkane derivatives which may be used as active ingredients in the pharmaceutical compositions of the invention there may be mentioned, for example, the known compounds N,N - dimethyl - 3,3 - diphenylpropylamine, N - methyl - 3,3 - diphenylpropylamine, and N - ethyl - N - methyl - 3,3 - diphenylpropylamine, and the new compounds: N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl)-3 - phenylpropylamine, N,N - dimethyl - 3-(4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3-phenylpropylamine, N,N - dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3 - (2 - methoxyphenyl) - 3-phenylpropylamine, N,N - dimethyl - 3,3-bis - (4 - chlorophenyl)propylamine, N,N-dimethyl - 3 - (4 - chlorophenyl) - 3 - (4-fluorophenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - fluorophenyl)propylamine, N-methyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N-dimethyl - 3 - (3 - trifluoromethylphenyl) - 3-phenylpropylamine, and acid-addition salts thereof.

[*Price 4s. 6d.*]

As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

Suitable pharmaceutically-acceptable diluents or carriers for use as excipients in the compositions of the invention are those known to the art and used in the preparation of pharmaceutical formulations for human and veterinary medication.

The pharmaceutical compositions of the invention include compositions which are suitable for oral administration. These include, for example, solid compositions, for example tablets, pills, capsules, dispersible powders and granules, which may optionally be coated, for example with a sweetening agent and/or a protective material designed to modify the distribution and absorption of the active ingredient or ingredients in the digestive tract. They also include orally-administerable semi-solid or liquid formations, for example pharmaceutically-acceptable emulsions, syrups, dispersions and solutions, either for administration *per se* with or without flavouring agents or after confinement in some suitable way, for example in capsules.

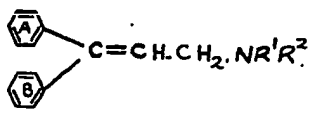
The pharmaceutical compositions of the invention also include liquid compositions which are sterile aqueous solutions, suspensions or emulsions, or sterile non-aqueous solutions or suspensions which can be administered by injection, for example intravenously, subcutaneously or intramuscularly. Those injectable compositions of the invention which are suspensions contain their particulate matter in a finely divided form, for example in a micro-pulverised form, and those compositions which are aqueous suspensions may optionally contain small amounts of such agents as are commonly used to facilitate the manufacture and maintain the efficacy of aqueous suspensions, for example dispersing and suspending agents.

Suitable vehicles for the non-aqueous solutions and suspensions of the invention include, for example, water-miscible non-toxic vehicles, for example propylene glycol and polyethylene glycol, and water-immiscible non-toxic vehicles, for example injectable vegetable oils, for example arachis oil, and oil-like injectable organic esters, for example dibutyl succinate. The said water-immiscible vehicles may also contain metallic soaps, for example aluminium stearate.

The sterile injectable solutions, suspensions or emulsions of the invention may be obtained sterile by known precedures, for example by aseptic formulation, by Seitz filtration, by irradiation, by the incorporation of sterilising agents in the compositions, or by heat treatment.

The compositions of the invention include pharmaceutical compositions which are sterile powders comprising the active ingredient or ingredients together with such non-toxic pharmaceutical excipients as are required to provide, on mixing with water, sterile aqueous solutions or suspensions suitable for parenteral administration.

The alkane derivatives which are used as the active ingredients in the pharmaceutical compositions of this invention may be obtained by the reduction of an alkene derivative of the formula:—



wherein A, B, R^1 and R^2 have the meanings stated above, or an acid-addition salt thereof, as described in our co-pending patent application No. 38195/66 (Serial No. 1,169,944) of even date herewith, or by analogous means.

The invention is illustrated but not limited by the following Example in which the parts are by weight:—

EXAMPLE

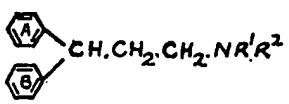
A mixture of 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride, 125 parts of maize starch, 270 parts of calcium phosphate and 1 part of magnesium stearate is compressed, and the compressed material is then broken down into granules by passage through a 16-mesh screen. The granules so obtained are then compressed into tablets which are suitable for oral administration for therapeutic purposes.

In place of the 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride used in the above example there may be used 25 parts of any of the following compounds:—

N - methyl - 3,3 - diphenylpropylamine hydrocloride, N - ethyl - 3,3 - diphenylpropylamine hydrochloride or N - ethyl - N-methyl - 3,3 - diphenylpropylamine hydrochloride. It is to be understood that the pharmaceutical compositions claimed in the following claims do not include simple solutions of the alkane derivatives(s) in question in common solvents for example water.

Subject to this disclaimer, WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising at least one alkane derivative of the formula:—



wherein R^1 stands for hydrogen or an alkyl radical, R^2 stands for an alkyl radical, and either or both of the phenyl radicals A and B

may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

2. A composition as claimed in claim 1 wherein R^1 stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R^2 stands for an alkyl radical of not more than 6 carbon atoms, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radicals, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

3. A composition as claimed in claim 1 wherein R^1 stands for hydrogen or the methyl radical, R^2 stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

4. A composition as claimed in claim 3 wherein the halogen substituent(s) is or are selected from fluorine and chlorine atoms.

5. A composition as claimed in claim 1 in which the active ingredient is N,N - dimethyl-3,3 - diphenylpropylamine or an acid-addition salt thereof.

6. A composition as claimed in claim 1 in which the active ingredient(s) is or are selected from N - methyl - 3,3 - diphenylpropylamine, N - ethyl - N - methyl - 3,3 - diphenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N-dimethyl - 3,3 - bis - (4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - fluorophenyl) propylamine, N - methyl - 3,3 - bis - (4-fluorophenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

7. A composition as claimed in any of claims 1 to 6 which is in the form of a tablet, pill, capsule, dispersible powder or granule, emulsion, syrup, dispersion, non-sterile solution, or a sterile injectable aqueous solution, suspension or emulsion or a sterile injectable non-aqueous solution or suspension, or a sterile powder.

8. A tablet, claimed in claim 7, substantially as described in the foregoing Example.

WALTER SCOTT,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/021271 A2

(51) International Patent Classification[7]: G01N 33/566, 33/50

(21) International Application Number: PCT/IB02/03618

(22) International Filing Date:
4 September 2002 (04.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0121440.2	4 September 2001 (04.09.2001)	GB
60/323,973	20 September 2001 (20.09.2001)	US

(71) Applicant *(for GB only)*: **PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB, US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GREENGRASS, Pamela, May** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **STEWART, Michael** [GB/GB]; Pfizer Limited, U.K. Patent Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **WOOD, Claire, Margaret** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: **HAYLES, James, R.** et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/021271 A2

(54) Title: ASSAY

(57) Abstract: The invention relates to an assay to establish the affinity of compounds at the "ether-a-go-go" (ERG) potassium (K+) channel, in particular the human ERG (hERG) potassium channel, using a labelled inwardly rectifying potassium channel (IKR) blocker. This assay is useful to identify compounds with undesirable effects on cardiac repolarisation in man, in particular the propensity to prolong the QT interval in the electrocardiogram.

Assay

The invention relates to an assay to establish the affinity of compounds at the "ether-a-go-go" (ERG) potassium (K^+) channel, in particular the human ERG (hERG) potassium channel, using a labelled rapid delayed rectifying potassium channel (IKR) blocker, for example [^{3}H]-dofetilide or [^{3}H]-MK-499. This assay is useful to identify compounds with undesirable effects on cardiac repolarisation in man, in particular the propensity to prolong the QT interval in the electrocardiogram, which may lead to Torsades de Pointes.

In recent years the development of some compounds proposed for therapeutic use has been abandoned in late phase drug development due to the detection of undesirable effects on cardiac repolarisation in man. The effects of these drugs are assessed in terms of the QT interval in the electrocardiogram (ECG). The QT interval is the portion of an ECG that represents the time from the beginning of ventricular depolarization to the end of ventricular repolarisation. Because the QT interval can be affected by heart rate lengthening with a decrease in heart rate and shortening with an increase in heart rate, the QT is often "corrected" for heart rate, resulting in the QT_C interval. In rare cases the administration of some drug molecules results in a prolongation of the QT interval of the ECG in man. The ECGs of these patients resemble those of individuals suffering from an inherited disorder known as long QT syndrome. Drug-induced ventricular fibrillation, in these cases, can eventually lead to sudden death (Morganroth J et al. (1993) Am J Cardiol. 72, 26B-31B; De Ponti F. et al., (2000) Eur J. Clin. Pharmacol. 56, 1-18). A number of drug molecules, including, E-4031, cisapride and terfenadine, are all known to prolong the QT interval of the electrocardiogram in man (Fuliki A, *et al.* (1994), Cardiovascular Pharmacol. 23: 374-378; Van Haarst AD et al., (1998) Clin Pharmacol. Ther. 64: 542-546; Honig P.K. et al. (1993) J.A.M.A. 269; 1513-1518).

The launch of new drugs with undetected potentially cardiotoxic side effects could have hazardous consequences and could trigger lethal cardiac dysrhythmias in patients. Late detection of QT prolongation, induced by compounds of pharmacological interest can impede drug discovery and development programs, and consequently have a

profound impact on the outcome of a program. It is desirable, therefore, to test for the potential cardiotoxic side effects of compounds at an early stage of drug development.

According to the invention there is provided an assay that comprises, or consists of, the following steps:

a) incubation of cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG with labelled IKR blocker in assay buffer in the presence or absence of different amounts of a test compound or a mixture of test compounds;

b) determination of specifically bound labelled IKR blocker;

c) calculation of the inhibition of labelled IKR blocker binding by the test compound or mixture of test compounds.

The assay is useful as a preclinical predictive indicator for identification of compounds with a propensity to prolong the QT interval in man. The assay is a competitive binding assay that measures the ability of a test compound or mixture of compounds to displace labelled IKR blocker from the ERG K^+ channel (ether-a-go-go K^+ channel, herein called ERG). The assay can be performed in a high throughput test system. In conjunction with structure-activity relationships (SAR), ligand binding assays using labelled IKR blockers can be used to assist in the design of new drugs devoid of, or with reduced affinity to ERG, in particular human ERG (hERG).

The assay buffer used is particularly important for optimising binding of the IKR blocker or test compound(s) to ERG. It has been found that optimal assay performance is achieved using a Tris based buffer (pH 7.2 to 7.6, preferably pH 7.4 at room temperature) containing potassium (K^+) ions. Potassium ions in the assay buffer may be provided, for example as potassium choride (KCl). The concentration of potassium ions in the assay buffer determines the predictive value of the assay. Assays performed in assay buffer containing from 7.5 to 12.5mM KCl, preferably from 8.5 to 11.5mM KCl, most preferably 10mM KCl are particularly useful to provide an IC_{20} value predictive of onset of QT prolongation.

The assay buffer of the invention preferably comprises or consists of Tris.Cl and KCl. Optionally, $MgCl_2$ may be included in the assay buffer.

The concentration of Tris.Cl in the assay buffer is preferably from 30mM to 100mM Tris.Cl, more preferably from 30mM to 70mM Tris.Cl, yet more preferably from 40mM to 60mM Tris.Cl, further preferably from 45mM to 55 mM Tris.Cl, most preferably 50mM Tris.Cl.

The concentration of KCl in the assay buffer is preferably from 5 to 20mM KCl, more preferably from 6 to 15mM KCl, yet more preferably from 7.5 to 12.5mM KCl, further preferably from 8.5 to 11.5mM KCl, most preferably 10mM KCl.

In a particularly preferred embodiment, the assay buffer comprises or consists of from 30 to 100mM Tris.Cl and from 5 to 20mM KCl, preferably from 30 to 70mM or from 30 to 100mM Tris.Cl and from 6 to 15mM KCl; yet more preferably from 40 to 60mM Tris.Cl and from 7.5 to 12.5mM KCl; further preferably from 45 to 55mM Tris.Cl and from 8.5 to 11.5mM KCl.

It is particularly preferred that the assay buffer comprise or consist of 50mM Tris.Cl and 10mM KCl.

If $MgCl_2$ is included in the assay buffer, the concentration of $MgCl_2$ is preferably from 0.6mM to 2.0mM $MgCl_2$, more preferably from 0.6mM to 1.6mM $MgCl_2$, yet more preferably from 0.8mM to 1.4mM $MgCl_2$, further preferably from 0.9mM to 1.3mM $MgCl_2$, yet further preferably from 1.0mM to 1.2mM $MgCl_2$, most preferably 1.0mM or 1.2mM $MgCl_2$.

In a preferred embodiment the assay buffer used comprises or consists of from 30 to 100mM Tris.Cl, from 5 to 20mM KCl, and from 0.6 to 2.0mM $MgCl_2$; preferably from 30 to 100mM Tris.Cl or from 30 to 70mM Tris.Cl, from 6 to 15mM KCl, and from 0.6 to 1.6mM $MgCl_2$; yet more preferably from 40 to 60mM Tris.Cl, from 7.5 to 12.5mM KCl and from 0.8 to 1.4mM $MgCl_2$; further preferably from 45 to 55mM Tris.Cl, from 8.5 to 11.5mM KCl and from 0.9 to 1.3mM $MgCl_2$ or from 1.0 to 1.2mM $MgCl_2$.

The assay buffer may comprise or consist of 50mM Tris.Cl, 10mM KCl and 1.0mM $MgCl_2$; or 50mM Tris.Cl, 10mM KCl and 1.2mM $MgCl_2$.

It is preferred that the assay buffer be at a pH between 7.2 and 7.6 at room temperature; it is particularly preferred that the assay buffer be at pH 7.4 at room temperature.

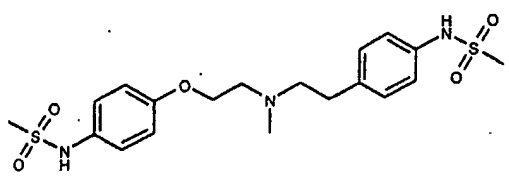
The ERG gene (cDNA) can be from a vertebrate or invertebrate source; for vertebrates the ERG gene may be from a mammalian source (e.g. human, simian, bovine, porcine, canine, rabbit, guinea pig, rat, or mouse) or an invertebrate source such as an insect source (e.g. drosophila). A prokaryotic homologue of mammalian ERG may be used. It is preferred that the ERG gene be mammalian ERG, in particular human ERG (hERG) or canine ERG (cERG).

The ERG gene may be expressed in a mammalian cell line e.g. HEK-293 (Human embryonic kidney) cells, CHO (Chinese hamster ovary) cells; CHL (Chinese hamster lung) cells, COS (monkey) cells; or in an insect cell line e.g. SF9. A baculovirus vector system can be used for expression of ERG in a compatible insect cell line. Alternatively, ERG may be expressed in yeast or bacterial cells. It is preferred that the ERG gene is hERG or cERG and is expressed in either HEK-293, CHO or CHL cells.

The assay may be performed using whole cells expressing ERG or membrane preparations derived from cells expressing ERG, or membrane preparations derived from tissue expressing ERG.

Dofetilide is an IKR blocker (selective inhibitor of the rapid component of the delayed rectifier potassium current), which prolongs the action potential duration and the effective refractory period in a concentration-dependent manner. Clinical studies have demonstrated that dofetilide is effective in treating patients with atrial as well as ventricular arrhythmias. Dofetilide has formula I below.

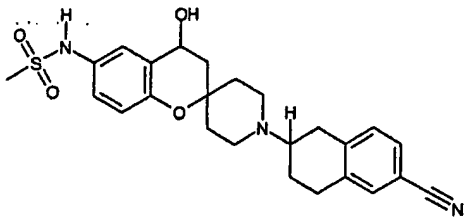
Formula I



Dofetilide is claimed and its preparation is described in European patent EP 0245997.

MK-499 (Merck) is methylsulphonamide antiarrhythmic drug that acts as an IKR blocker. MK-499 has formula II shown below.

Formula II



The IKR blocker used in the assay is labelled with a detectable label, for example a radiolabel or fluorescent tag. In a preferred embodiment of the invention, the labelled IKR blocker used in the assay is labelled dofetilide, preferably radiolabelled dofetilide, most preferably tritiated dofetilide ([^{3}H]-dofetilide). In another embodiment of the invention, the labelled IKR blocker used in the assay is labelled MK-499, preferably radiolabelled MK-499, most preferably tritiated MK-499 ([^{3}H]-MK-499).

Preferred assay formats include the filter binding technique, whereby bound and unbound labelled IKR blocker e.g. labelled dofetilide or labelled MK-499; preferably radiolabelled dofetilide or radiolabelled MK-499; most preferably [^{3}H]-dofetilide or [^{3}H]-MK-499, are separated by filtration. The assay can be performed utilising the scintillation proximity assay (SPA) technique, using radiolabelled IKR blocker e.g. radiolabelled dofetilide or radiolabelled MK-499, preferably [^{3}H]-dofetilide or [^{3}H]-MK-499.

In the filter binding technique, cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG are incubated in assay buffer with labelled IKR blocker e.g. [^{3}H]-dofetilide or [^{3}H]-MK-499, in the presence (test) or absence (control) of the test compound or mixture of test compounds. Incubations are preferably carried out at room temperature for from 60 to 120 minutes, preferably for 90 minutes. Non-specific binding is determined in the

presence of unlabelled IKR blocker, e.g. 10μM dofetilide or 10μM MK-499. Bound labelled IKR blocker is separated from unbound IKR blocker by filtration through filter mats, or onto multiwell filter plates. Filter mats or plates are washed to remove unbound labelled IKR blocker, bound labelled IKR blocker is quantified e.g. for tritiated IKR blocker such as [^{3}H]-dofetilide or [^{3}H]-MK-499 by scintillation spectroscopy using an appropriate counter for radioactivity.

In the scintillation proximity assay™ (SPA) system (Amersham Biosciences), beads are used to bind cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG. A variety of bead types are suitable for use in a SPA assay according to the invention, these include PVT wheat germ agglutinin, yttrium oxide polylysine beads, or yttrium silicate beads (YSi) (Amersham Biosciences) such as YSi polylysine or YSi wheat germ agglutinin. The optimum bead type for use in a SPA assay of the invention depends on the cells or cell membranes used; bead to cell or bead to membrane binding may be assessed to identify the optimum bead type for the cell or cell membrane used. Beads bound to ERG material (whole cell, cell membrane preparation or tissue membrane preparation) are incubated in assay buffer with labelled IKR blocker, e.g. [^{3}H]-dofetilide or [^{3}H]-MK-499 in the presence (test) or absence (control) of the test compound or mixture of test compounds. The ability of the test compound or mixture of test compounds to displace bound radiolabelled IKR blocker is determined by detecting light emissions, for example using standard counters that can be used with SPA technology.

The assay may also include one or more of the steps of: calculation of the concentration of the test compound(s) that gives 20% inhibition of dofetilide binding (IC_{20}), calculation of the concentration of the test compound(s) that gives 50% inhibition of dofetilide binding (IC_{50}), calculation of the compound affinity as Ki or calculation of the compound affinity as pKi.

The IC_{20} values generated from competitive displacement of IKR blocker binding, e.g. [^{3}H]-dofetilide binding, using the assay of the invention are comparable to the free drug concentration associated with QT prolongation in man. Thus the assay can be used to predict the concentration of a compound liable to cause undesirable cardiac side effects.

To assess whether a compound, or mixture of compounds, is likely to prolong the QT interval in the electrocardiogram in man, the following steps are carried out:

a) An assay is carried out according to the invention.

b) An IC_{20} value is obtained; this indicates the real or predicted free drug concentration at which QT prolongation will occur in man;

c) The IC_{20} value is compared with the free drug concentration required for the desired therapeutic effect of the compound or mixture of compounds in vivo.

If the free drug concentration required for the desired therapeutic effect of the compound or mixture of compounds is within 10 to 30 fold of the IC_{20} of the compound or mixture of compounds in the assay, the compound or mixture of compounds is likely to show QT interval prolongation in man.

The assay of the invention is a better predictor of *in vivo* QT prolongation effect of drug molecules than existing assays such as the HERG patch clamp assay.

List of Figures

Figure 1: Representative saturation curve data for [^{3}H]-dofetilide binding to HERG in (a) filter binding, (b) SPA 96 well format and (c) SPA 384 well format.

Figure 2: Correlation plots comparing p*K*i values obtained from filter binding and SPA binding assays: (a) correlation between 96 well hERG [^{3}H] dofetilide SPA assay and radioligand binding assay, (b) correlation between 96 well and 384 well hERG [^{3}H] dofetilide SPA assay.

Figure 3: Comparison of inhibition of [^{3}H]-dofetilide binding to hERG, hERG patch clamp, and free drug concentration known to induce QT interval prolongation in man, for (a) E-4031, (b) dofetilide, (c) terfenadine and (d) cisapride.

Figure 4: Comparison of the dofetilide IC_{50} in the dofetilide binding assay carried out in cell membranes from HEK-293 cells transfected with human ERG (hERG (▲)) or with canine ERG (cERG (■))

Figure 5: Comparison of terfenadine IC_{50} in the dofetilide binding assay in cERG or hERG transfected HEK-293 cell membranes

Figure 6: Comparison of E4031 IC_{50} in the dofetilide binding assay in cERG or hERG transfected cell HEK-293 membranes

Figure 7: Mean (n = 2) concentration effect curves for (a) dofetilide and (b) terodiline in tritiated dofetilide SPA assays using assay buffer 50mM Tris Cl, 10mM KCl, at pH7.4.

Examples

Example 1: Preparation of membranes from HEK-293 cells expressing human or canine ERG

An adherent HEK-293 cell line expressing human ERG (Zhou, Z et al (1998) Biophys. J. 74, 230-241) was provided by Dr. Craig January, University of Wisconsin, USA; this cell line was designated the "January" cell line. An alternative adherent HEK-293 cell line, designated cell line 15 (293S-HERG clone 15) was produced by the method described in Zhou, Z et al (1998). Full length cDNA for human ERG was inserted downstream of the CMV promoter in pcDNA3.1 (Invitrogen), the vector also has a SV40 promoter that drives expression of a neomycin resistance gene. The construct was transfected into human embryonic kidney 293S (HEK-293) cells. Stable transformants were selected using G418 (Gibco). Although cell line 15 has slightly lower expression of hERG than the January cell line, it has improved growth characteristics.

Cell line 15 (293S-HERG (Clone 15)) was deposited on 26 June 2002 with the ECACC (CAMR Salisbury, Wiltshire, SP4 OJG, UK) in accordance with the terms of the Budapest Treaty 1977 under deposit accession number 02062678.

Adherent HEK-293 cells expressing human ERG, were grown in MEM Earles medium (Life Technologies) supplemented with 10% foetal calf serum (PAA Laboratories), 2 mM L-glutamine (Sigma), 1 mM sodium pyruvate (Sigma), 0.4 mg/ml G418 (Life Technologies) and an addition of 1x non-essential amino acids (Life Technologies). The cells were grown at 37°C in a humidified atmosphere with 5% CO_2 in T225 cm^3 flasks.

The cells were split 1:3 to 1:5 after reaching 80% confluence using cell dissociation solution (Sigma, cat no: C5914 in 2001) and later seeded into 850 cm^2 CO_2 gassed roller bottles (Corning, cat no: 430849 in 2001) in the absence of G418.

For the preparation of membranes, cells were harvested from the roller bottles by scraping and resuspended in PBS (Life Technologies, cat no: 14190-094 in 2001). All cells were pelleted, washed twice with PBS and snap-frozen on dry ice prior to storage at –80°C until required.

A HEK-293 cell line expressing canine ERG was produced by transient transfection of HEK-293 cells. The complete coding sequence of cERG cDNA (Zehelein et al (2001). Pflugers Archiv. European Journal of Physiology. 442(2): 188 – 191) was provided in the pBluescript® vector (Stratagene) by Professor Zehelein University of Heidelberg, Germany. In the pBluescript construct, the cERG cDNA was flanked by *Bam*HI Sites. Initial experiments indicated poor insertion efficiency for direct insertion of cERG *Bam*HI fragment into the desired vector, pcDNA3.1. To overcome this, an indirect cloning method was devised using the cloning vector pSP73 (Promega). The cERG/pBluescript construct and pSP73 vector were subjected to *Bam*HI digestion, to reduce interference by the presence of pBluescript *Bam*HI fragments in the ligation reaction, the cERG/pBluescript *Bam*HI digested material was also subjected to *Sca*I digestion to cleave pBluescript and ensure more effective separation of the cERG *Bam*HI fragment on agarose gel. The restriction mixtures were subjected to agarose gel electrophoresis, bands containing the cERG and pSP73 *Bam*HI fragments were visualized following staining with ethidium bromide and UV illumination. The cERG and pSP73 bands were excised and eluted from the gel using a QIAgen MinELute Gel extraction kit according to the manufacturers instructions. To prevent religation of the *Bam*HI ends of the pSP73 DNA during the ligation reaction, the plasmid DNA fragments were subjected to CIP treatment using a standard protocol. The cERG *Bam*HI fragments were ligated into the pSP73 *Bam*HI fragments using a standard ligation protocol. After the reaction, the ligation mixture was transformed into cJM109 competent *E. coli* cells using a standard transformation protocol. Transformants were selected by plating on LB agar (Millers) containing ampicillin (50µg/ml) and incubated overnight at 37°C. Overnight cultures of the transformed cells were used to produce mini preparations of cERG/pSP73 DNA using a QIAgen Miniprep kit according to the

manufacturer's instructions. The resulting DNA was subjected to restriction digestion and agarose gel electrophoresis to identify positive clones.

The cERG cDNA was excised from cERG/pSP73 as an *Xho*I (5') *Eco*RI (3') fragment, this fragment was ligated into an *Xho*I/*Eco*RI fragment of the reverse poly linker form of pcDNA3.1, pcDNA3.1(-) *Xho*I/*Eco*RI. In this instance the reverse polylinker form was used because the cERG/pSP73 clone selected contained the reverse orientation of cERG. After ligation into pcDNA3.1(-), the 5' end of cERG was located adjacent to the enhancer-promoter sequence from human cytomegalovirus (CMV). The ligation mixture was transformed into cJM109 competent *E. coli* cells using a standard transformation protocol, transformants were selected via plating onto LB agar (Millers) containing ampicillin (50µg/ml) and incubating overnight at 37°C along with required controls. Colonies picked at random from the cERG/pcDNA3.1(-) plates were inoculated into 5ml of LB media containing ampicillin (50µg/ml) and incubated at 37°C, 200rpm overnight. These overnight cultures were subsequently used to produce mini-preps of DNA using a QIAgen Miniprep Kit. The resulting DNA was subjected to a *Xho*I and *Eco*RI double digestion and analysis on 1% agarose gel. No positive cERG/pcDNA3.1(-) clones were identified because of low insertion efficiency in the ligation reaction coupled with the fact that DNA from only a small number of clones was analysed using the mini prep method. A colony PCR method was thus used to screen a larger number of colonies for positive clones.

The colony PCR protocol permitted rapid detection of cERG/pcDNA3.1(-) clones. Three primers were designed and made for use in the PCR protocol:

Primer 1: 'CERG01' (SEQ ID NO: 1) which hybridises to cERG at nucleotide positions 601-620 of the coding sequence:

5'-ACCACATCCACCAGGCACAG-3'

Primer 2: 'NHE PCDNA3' (SEQ ID NO: 2) which hybridises to pcDNA3.1(-) at nucleotide positions 886-910 (within the multicloning site flanking the *Nhe*1 cloning site):

5'-CCCAAGCTGGCTAGCGTTTAAACGG-3'

Primer 3: 'T7 SP73' (SEQ ID NO: 3) which was used as a control and used against a colony known to produce cERG/pSP73. This hybridised to pSP73 at nucleotide positions 98-121, within the T7 polymerase promoter sequence:

5'-TAATACGACTCACTATAGGGAGA-3'

Ninety-five cJM109 colonies were picked from the LB agar transformation plates and transferred to a sterile deep well 96-well plate containing 1ml/well LB broth supplemented with ampicillin (50µg/ml). As a control, a colony known to contain the cERG/pSP73 plasmid was transferred to the final 96th well containing LB-amp broth. The plate was covered and incubated at 37°C overnight at 200rpm. An aliquot of 70µl of each mini-culture was transferred to a 96-well PCR plate (0.5ml/well) and placed in a Beckman Allegra 6R centrifuge for 2800rpm, room temperature for 10 minutes. The supernatant was discarded and the plate drained for 3 minutes. The PCR reaction mixes were set up and added to the PCR plate containing the bacterial pellets as follows:

	Test wells	Control well cERG/pSP73
Taqman Gold buffer (X10)	10.0µl	10µl
dNTPs (X10, 2mM/dNTP)	2.0µl	2µl
Taqman Gold Polymerase (5u/µl)	0.5µl	0.5µl
CERG01 (primer 1- 25µM)	2µl	2µl
NHE PCDNA3 (primer 2- 25µM)	2µl	-
T7 SP73 (primer 3- 25µM)	-	2µl
Nuclease free water	83.5µl	83.5µl

The bacterial pellet was resuspended in the PCR reaction mixture. The PCR reaction was performed as specified by the manufacturers protocol for the Taqman Gold PCR kit (Applied Biosystems, 1999 edition) thus:

	Temperature	Time	
Step 1 - hot start	95°C	6 minutes	
Step 2 - denaturation	95°C	1 minute	
Step 3 - annealing	60°C	1 minute	
Step 4 - extension	72°C	1 minute	*To step 2 for 35 cycles, then step 5.*

Step 5 - denaturation	95°C	45 secs
Step 6 - annealing	60°C	45 secs
Step 7 - extension	72°C	5 minutes

The PCR products for each well were then separated by electrophoresis on a 1.5% agarose gel using a 100bp DNA ladder marker at 100V for 25 minutes in 1X TAE buffer and visualised using UV light. Putative positive clones were identified and samples from these PCR reaction mixtures were run on a second separate 1.5% agarose gel at 100V for one hour to examine the sizes of the PCR products.

The mini-cultures which gave an amplified a PCR product were each seeded from the original deep-well 96-well plate into sterile tubes with 5ml LB broth containing 50µg/ml ampicillin and incubated at 37°C overnight at 200rpm. The overnight cultures were then used to produce mini-preps of DNA using a QIAgen Miniprep Kit. The resulting DNA was subjected to an *Xho*I and *Eco*RI double digestion to check for the presence of cERG/pcDNA3.1(-). The restriction digest was analysed via a 1% agarose gel run for 1 hour at 100V with 1kb DNA ladder markers (20µl sample loading with 2µl gel loading solution). Further restriction digestion analysis was performed to confirm that the purified plasmids from the transformants were indeed cERG/pcDNA3.1(-).

Untransfected HEK-293 cells were routinely maintained in 50ml Minimum Essential Medium (MEM) supplemented with 10% (v/v) foetal calf serum (FCS), 2mM L-glutamine, 1mM sodium pyruvate and 1mM non-essential amino acids. Cells were seeded into 225cm^2 ventilated cap flasks and were maintained in a humidified atmosphere containing 5% CO_2. The HEK-293 cells used in this study were between passage numbers 39-48. Cells were passaged typically every three days in a ratio of 1:3 from a flask of 80-90% confluency; fresh medium was added after washing twice with 10ml PBS and dissociating from the flask using cell dissociation fluid.

The cERG/pcDNA3.1(-) construct was transfected into HEK-293 cells grown to 80-95% confluency in 225cm^2 ventilated flasks using the following method. Endotoxin free cERG/pcDNA3.1(-) DNA (94µg) and Lipofectamine2000 (Gibco BRL) (94µg) were added to 2.25ml of OPTIMEM-I media (Gibco BRL) in sterile 10ml centrifuge tubes; mixing was carried out after incubation at room temperature for five minutes. The

Lipofectamine2000/DNA/OPTIMEM-I mix was then incubated at room temperature for twenty minutes before the addition of a further 10.5ml OPTIMEM-I. HEK-293 cells were washed with 10ml PBS and the Lipofectamine2000/DNA/OPTIMEM-I mixture added and incubated for 3.5 hours at 37°C in a humidified atmosphere containing 5% CO_2. After incubation, 50ml of MEM (supplemented with 10% (v/v) FCS, 2mM L-glutamine, 1mM sodium pyruvate and 1mM non-essential amino acids) was added. The HEK-293 cells were incubated for 24 hours at 37°C. Transfected cells were harvested after 24 hours by washing with PBS, scraping the cells into 10ml PBS and centrifuging at 1000rpm for 5 minutes at room temperature. The resulting cERG/pcDNA3.1(-) transfected HEK-293 cell pellet was stored at -80°C until required.

Preparation of membranes from HEK-293 cells expressing human or canine ERG

Cell membrane fractions were prepared from frozen aliquots of cells. All procedures were carried out at 4°C unless otherwise stated. Frozen aliquots of cells were thawed at room temperature and resuspended in assay buffer (e.g. 50mM Tris.Cl, 10mM KCl, 1 to 1.2mM $MgCl_2$, pH7.4, or 50mM Tris.Cl, 10mM KCl, pH7.4). The cells were then disrupted by homogenisation in an Omni LabTek homogeniser at 20,000 rpm for 30 seconds. The homogenate was centrifuged for 20 minutes at 48,000xg (4°C, Sorvall RC5B centrifuge) and the supernatant removed. The resulting pellets were resuspended in assay buffer and homogenised as above for 10 seconds. The pellets were collected by centrifugation and the final pellet resuspended in assay buffer. Protein content was determined using a Coomassie Blue based protein assay kit. Aliquots were stored at -80°C until needed; when stored in these conditions, the binding ability of the cell membrane fractions proved to be stable for at least 4 months.

Example 2: Filter binding assay with [^{3}H]-dofetilide

[^{3}H]-dofetilide (80-83 Ci/mmol) was synthesized by catalytic tritiation (a custom service provided, for example, by Amersham Life Science). However, other detectable labels known to the skilled person can be used instead of ^{3}H, e.g. fluorescent tags, other radiolabels, antibodies etc.

On the day of the assay, test compounds were dissolved at 1 mM in 50% DMSO or 100% DMSO, and then diluted to the desired concentrations (e.g. up to 100μM, or up to

the boundaries of solubility for the compound) in assay buffer. The final DMSO concentration in assay incubations is preferably 1.0 to 1.5% or less for optimal assay conditions.

Incubations included membrane homogenate at 50µg/ml in assay buffer (50 mM Tris.Cl, 10mM KCl, 1.0mM to 1.2mM $MgCl_2$, pH7.4) unless otherwise indicated, [^{3}H]-dofetilide (4 to 7nM) and test compound or mixture of test compounds or control vehicle. Filtration assays were incubated at room temperature for 90 minutes. Non-specific binding was determined in the presence of 10 µM dofetilide and was usually less than 15 % of total binding. Bound ligand was separated from free ligand by rapid filtration through GF/B glass fibre filter mats using, for example, a Brandel cell harvester, or onto GF/B Unifilter 96-well filter plates (Packard) using a Packard Filtermate 96 harvester. Filter mats and plates were pre-soaked in 5% PEI (w/v) for 60 minutes and washed after harvesting with 3 x 1 ml washes of ice-cold assay buffer. Unifilter plates were air dried for a minimum of 1.5 hours at 37°C prior to the addition of Microscint-0 (Packard). Bound [^{3}H]-dofetilide was determined by liquid scintillation spectroscopy using an appropriate counter, for example in a Packard TopCount Scintillation Counter (NXT Counter) or Wallac Counter (Trilux) for Unifilter plates and in a Wallac Big Spot Counter when filter mats were used.

In each experiment, triplicate assays were routinely performed and the data were averaged. Specific binding was analysed by nonlinear regression fit using GraphPad Prism software (GraphPad, San Diego). IC_{50} values were derived from a 4 parameter logistic fit using PRISM and converted to K*i* values by use of the Cheng & Prusoff equation; IC_{20} values were extrapolated from the graph.

Example 3: Scintillation proximity assay

The scintillation proximity assay (SPA) was carried out in assay buffer consisting of 50mM Tris.Cl, 10mM KCl, 1.0mM to 1.2mM $MgCl_2$, pH7.4, or using assay buffer consisting of 50mM Tris base, 10mM KCl, pH7.4. Bead to membrane binding was assessed to determine the optimum bead type for the cell line used. YSi wheatgerm agglutinin beads were used with cell membranes derived from the January HEK-293 hERG expressing cell line; YSi polylysine beads were used in studies using membranes

derived from Cell Line 15 (HEK-293 hERG expressing cell line). Conditions were optimised with respect to bead and cell membrane homogenate concentration, prior to characterising ERG pharmacology. The incubations (200 µl total per well for 96 well plates and 60 µl total per well for 384 well plates) included 25 µg of cell membrane homogenate per mg of bead. The membrane homogenate was precoupled with the YSi Wheatgerm Agglutinin or YSi polylysine bead suspension at 4°C on a roller shaker for approximately 2 hours. For competition binding assays, membrane homogenate bead suspension was incubated in white clear bottom 96 or 384 well plates with 5nM [^{3}H]-dofetilide in the absence and presence of competitor i.e. the test compound or mixture of test compounds. The plates were incubated at room temperature and shaken for approximately 1 hour. Beads were allowed to settle for a minimum of 30 minutes before plates were counted for retained radioactivity on a TopCount NXT scintillation counter. Nonspecific binding i.e. background count, was determined by the addition of 10µM dofetilide. Background counts were usually less than 15% of the total binding. For saturation studies, specific binding of [^{3}H]-dofetilide was determined over a range of concentrations (5 to 500nM) in the absence or presence of cold (i.e. unlabelled) 10µM dofetilide.

Example 4: Assay optimisation

a) Effect of Hepes- and Tris-based buffers on dofetilide binding

To optimise the specific binding of dofetilide to homogenates of cell membranes containing ERG, the interaction of [^{3}H]-dofetilide with the cell membrane preparation was examined in the presence of Hepes-based buffer (25mM Hepes, 135mM NaCl, 5mM KCl, 1mM $MgSO_4$, 50mM $CaCl_2$, pH7.4) and Tris-based buffer (50mM Tris.Cl, 10mM KCl, 1mM or 1.2mM $MgCl_2$). Comparison of the specific binding in these buffers revealed that percentage specific binding was similar in both Tris-based and Hepes-based buffers. However, as shown in Table 1, specific counts were twice as high in the presence of Tris-based buffer compared to those detected in Hepes-based buffer.

Table 1. Comparative effects of Tris-based and Hepes-based buffers on [^{3}H]-dofetilide binding to cell membrane homogenate expressing hERG.

Buffer	25mM HEPES free acid 135mM NaCl, 5mM KCl 1mM $MgSO_4$, 50 µM $CaCl_2$ pH 7.4 at room temp	50mM Tris 10mM KCl and 1.0 or 1.2mM $MgCl_2$ pH 7.4 at room temp
Total Binding (ccpm)	6510 ± 669	19627 ± 1189
Non-specific Binding (ccpm)	321 ± 27	315 ± 23
Specific Binding (ccpm)	8189	19312
% Specific Binding	96	98

Total and non-specific binding data represent arithmetic mean ± standard error mean of 14 individual wells per buffer split over two assays, performed at a protein concentration of 75µg/ml and a mean [^{3}H]-dofetilide concentration of 6.7nM. Incubation was carried out for 60 minutes at room temperature. ccpm=corrected counts per minute.

So that the maximum specific binding window could be achieved, the assay buffer used in Examples 1 to 8 was the Tris-based incubation buffer (50mM Tris.Cl, 10mM KCl, 1mM $MgCl_2$). Additionally, experiments were performed to optimise the cell membrane protein concentration and bead concentration for filter and SPA binding assays.

b) Saturation binding

Time courses were performed to determine optimal incubation time for binding activities. Incubation times were similar for both filter binding and SPA assays. The filter binding assay reached equilibrium in 90 minutes, SPA required 60 minutes. [^{3}H]-dofetilide binding to ERG in both filter binding and scintillation proximity assays was saturable with a K_D of 5.08 ± 1.0nM for filter binding and K_D values of 8.9 ±0.6nM and 9.1 ±1.8nM for 96 and 384 format scintillation proximity assays respectively (Figure 1a-c, with Fig. 1a showing the results of the filter binding assay, Fig. 1b the results of the SPA in 96-well format, and Fig. 1c showing the results of the SPA in 384 well format). Non-linear curve fitting of this data indicated that binding was to a single site. A B_{max} of 7.4 ± 0.7pmol/mg protein for [^{3}H]-dofetilide was obtained from filter binding (Figure 1). As scintillation proximity assays do not give an accurate determination of dpm (disintegrations per minute) values, a B_{max} is not quoted for SPA.

c) Comparison of SPA and filter binding techniques

A comparison of SPA and filter binding techniques revealed excellent concordance of results. Affinity values displayed excellent correlation between the two assay types and the rank order of compound affinity is identical, as is shown in Figure 2 (correlation plots comparing p*K*i values obtained from filter binding and SPA binding assays).

d) Competitive binding studies

A range of compounds, including hERG blockers known to prolong the QT interval in man, was examined for competitive displacement of [^{3}H]-dofetilide. E4031, dofetilide, terfenadine, and cisapride produced complete inhibition of specific binding with a range of calculated affinity values that are summarised in Table 2.

Table 2. Affinity values for compounds tested against [^{3}H]-dofetilide filter and SPA binding assays to HERG.

Compound	Filter binding	SPA 96	SPA 384
	p*K*i	p*K*i	p*K*i
Dofetilide	8.22 ± 0.04	8.05 ± 0.54	8.26 ± 0.12
E4031	7.82 ± 0.03	7.81 ± 0.05	7.89 ± 0.11
Terfenadine	7.53 ± 0.09	7.75 ± 0.07	7.72 ± 0.41
Cisapride	7.34 ± 0.05	7.15 ± 0.04	7.55 ± 0.22
Glibenclamide	< 5	< 5	< 5
D-Sotalol	< 5	< 5	< 5

Data expressed as p*K*i values (the negative logarithm of molar concentration of competing ligand to displace 50% of 5nM [^{3}H]-dofetilide binding). Data are the mean of at least n = 3 experiments.

Example 5: Prediction of QT interval prolongation effect of compounds in man

The IC_{20} values generated from competitive displacement of [^{3}H]-dofetilide binding using the assay of the invention are comparable to the free drug concentration associated with QT prolongation in man as is shown in Figure 3 for a range of compounds, including E-4031 (Figure 3a), dofetilide (Figure 3b), terfenadine (Figure 3c) and cisapride (Figure 3d). For each compound, the inhibition of dofetilide binding in the binding assay (filter binding technique), and in a hERG patch clamp assay is compared with the concentration of free drug associated with QT interval prolongation in man (Fuliki A, *et al.* (1994) Cardiovascular Pharmacol, 23: 374-378; Van Haarst AD et al. (1998) Clin Pharmacol. Ther. 64: 542-546; Honig PK, et al. (1993) J.A.M.A. 269: 1513-1518).

The ERG patch clamp assay provides a measure of the current through the ERG channel and indicates the number of ion channels present in a cell. However, due to the phenomena of state dependent block observed in patch clamp studies (Walker, B.D. et al (1999) British J. Pharmacol 128, 444-450) exhibited by a number of known hERG blockers with the propensity to prolong the QT interval *in vivo*, the ligand binding assay provides a better predictor of *in vivo* QT prolongation effect of a drug than the hERG patch clamp technique (Figure 3d).

To assess whether a compound or mixture of compounds is likely to prolong the QT interval in the electrocardiogram in man, the following steps are carried out:

a) A binding assay is carried out according to the invention, for example as as described in Example 2 or Example 3, to test the affinity of the compound or mixture of compounds for ERG, preferably hERG or cERG;

b) The IC_{20} is obtained, e.g. as described at the end of Example 2; the IC_{20} being the real or predicted free drug concentration at which QT prolongation occurs in man;

c) The IC_{20} value is compared with the free drug concentration required for the desired therapeutic effect of the compound in vivo.

If the free drug concentration required for the desired therapeutic effect of the compound is within 10 to 30 fold of the IC_{20} of the compound in the assay of the invention, the compound is highly likely to cause QT interval prolongation in man.

Example 6: Comparison of dofetilide binding assay carried out HEK-293 cells transfected with cERG or hERG.

The dofetilide binding assay was carried out as described Example 2 using HEK 293 cells transfected with either human ERG or canine ERG. The results are shown in figure 4, from which it can be seen that the IC_{50} for dofetilide is similar for canine and human ERG, being 13.9nM and 15.6nM respectively. IC_{20} values for dofetilide were 1.92nM and 2.15nM for canine and human ERG, respectively.

Example 7: Comparison of terfenadine competition assay using HEK-293 cells transfected with cERG or hERG

The dofetilide binding assay was carried out using terfenadine as the test compound. Transiently transfected cERG HEK-293 cell membranes (200µg/well), or stable hERG HEK-293 cell membranes (100µg/well) were incubated with twelve different concentrations of terfenadine and 5nM [^{3}H]-dofetilide for 90 minutes at room temperature. Total and non-specific binding were measured by incubating with 10% DMSO and 10µM unlabelled dofetilide to a total assay volume of 200µl. The membranes were harvested by filtration with a Packard Unifilter cell harvester and radioactivity (cpm) was measured. Two saturation experiments were carried out each for cERG and hERG expressing cell membrane samples. Each experiment was carried out in triplicate. Figure 5 shows the mean values of the experiments for each cell type (cERG or hERG transfected) and indicates that the IC_{50} for terfenadine is similar for cERG and hERG, being 77.2nM and 88.9nM respectively. IC_{20} values for terfenadine were 10.7nM and 12.3nM for canine and human ERG, respectively.

Example 8: Comparison of E4031 competition assay in HEK-293 cells transfected with cERG or hERG

The dofetilide binding assay was carried out using E4031 as the test compound. Transiently transfected cERG HEK-293 cell membranes (200µg/well) or stable hERG HEK-293 cell membranes (100µg/well) were incubated with twelve different concentrations of E4031 and 5nM [^{3}H]-dofetilide for 90 minutes at room temperature. Total and non-specific binding values were measured by incubation with 10% DMSO and 10µM unlabelled dofetilide in a total assay volume of 200µl. The membranes were harvested by filtration with a Packard Unifilter cell harvester and radioactivity (cpm) was measured. Two saturation experiments were carried out each for cERG and hERG expressing cell membrane samples. Each experiment was carried out in triplicate. Figure 6 shows the mean values of the experiments for each cell membrane type (cERG or hERG transfected) and indicates that the IC_{50} for E4031 is similar for cERG and hERG, being 27.3 nM and 35.4 nM respectively. IC_{20} values for E4031 were 3.8 nM and 4.9 nM for canine and human ERG, respectively.

When IC_{50} (or IC_{20}) values are compared for the compounds tested, they were found to be very similar for cERG and hERG. This indicates that either hERG or cERG can be used in the assay of the invention to predict the onset of QT prolongation in man.

Example 9: Further assay optimisation studies

To further optimise the assay for specific binding of dofetilide to homogenates of cell membrane containing hERG, the interaction of [^{3}H]-dofetilide with cell membrane preparations was examined in the SPA assay format using a Tris based buffer containing either KCl or $MgCl_2$. SPA assays were performed according to example 3 in 50mM Tris.Cl, 10mM KCl at pH7.4 or in 50mMTris.Cl, 1mM $MgCl_2$ at pH 7.4 as the assay buffer. Assays were performed using dofetilide or terodiline as the test compound. Comparison of specific binding detected in these buffer conditions revealed that specific binding was not observed when the assay buffer used was 50mMTris.Cl, 1mM $MgCl_2$ at pH 7.4; specific binding was observed in assay buffer consisting of 50mM Tris.Cl, 10mM KCl at pH7.4. For the assays carried out in 50mM Tris.Cl, 10mM KCl at pH7.4 as the assay buffer the IC_{50} and IC_{20} values were generated for each test

compound. The mean IC_{50} value for dofetilide was 8.69± 0.45nM, the mean IC_{50} value for terodiline was 1.87 ± 0.00 μM. The mean IC_{20} value for dofetilide was 1.2nM, the mean IC_{20} value for terodiline was 0.248μM.

Sequence Listing Information

<110> Pfizer Inc (CA, EP except EP(GB), JP, US. Pfizer Ltd (EP(GB))

<120> Assay

<130> PCS 22042

<150> GB 0121440.2
<151> 2001-09-04

<150> US 60/323973
<151> 2001-09-20

<160> 3

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 20
<212> DNA
<213> Canine

<400> 1
accacatcca ccaggcacag 20

<210> 2
<211> 25
<212> DNA
<213> pcDNA3.1(-) vector

<400> 2
cccaagctgg ctagcgttta aacgg 25

<210> 3
<211> 23
<212> DNA
<213> pSP73 vector

<400> 3
taatacgact cactataggg aga 23

Claims

1. An assay comprising or consisting of the following steps:
(a) incubation of cells expressing ERG, or membranes derived from cells expressing ERG, or membranes derived from tissue expressing ERG, with labelled IKR blocker in assay buffer in the presence or absence of a test compound or a mixture of test compounds;
(b) determination of specifically bound labelled IKR blocker;
(c) calculation of the inhibition of labelled IKR blocker binding by the test compound or mixture of test compounds.
2. An assay according to claim 1, wherein the assay buffer is a Tris based buffer containing KCl.
3. An assay according to claim 2, wherein the assay buffer comprises or consists of from 30 to 100mM Tris.Cl, from 5 to 20mM KCl, and optionally from 0.6 to 2.0mM $MgCl_2$.
4. An assay according to claim 2, wherein the assay buffer comprises or consists of from 30 to 70mM Tris.Cl, from 6 to 15mM KCl, and optionally from 0.6 to 1.6mM $MgCl_2$.
5. An assay according to claim 2, wherein the assay buffer comprises or consists of from 40 to 60mM Tris.Cl, from 7.5 to 12.5mM KCl and optionally from 0.8 to 1.4mM $MgCl_2$.
6. An assay according to claim 2, wherein the assay buffer comprises or consists of from 45 to 55mM Tris.Cl, from 8.5 to 11.5mM KCl and optionally from 0.9 to 1.3 mM $MgCl_2$ or from 1.0 to 1.2mM $MgCl_2$.
7. An assay according to claim 2, wherein the assay buffer comprises or consists of 50mM Tris and 10mM KCl.
8. An assay according to claim 2, wherein the assay buffer comprises or consists of 50mM Tris, 10mM KCl and 1.0mM $MgCl_2$; or 50mM Tris, 10mM KCl and 1.2 mM $MgCl_2$.
9. An assay according to any one of the preceding claims wherein the assay buffer is at a pH between pH7.2 and pH7.6 at room temperature.
10. An assay according to claim 9, wherein the assay buffer is at pH7.4.
11. An assay according to any one of the preceding claims wherein the ERG is human ERG.

12. An assay according to any one of the preceding claims, wherein the labelled IKR blocker is labelled dofetilide or labelled MK-499.

13. An assay according to claim 12, wherein the labelled dofetilide or labelled MK-499 is radiolabelled.

14. An assay according to claim 13, wherein the radiolabel is tritium (^3H).

15. An assay according to any one of the preceding claims having the following additional step(s):

(d) calculation of the IC_{20} for the test compound or mixture of test compounds, and optionally,

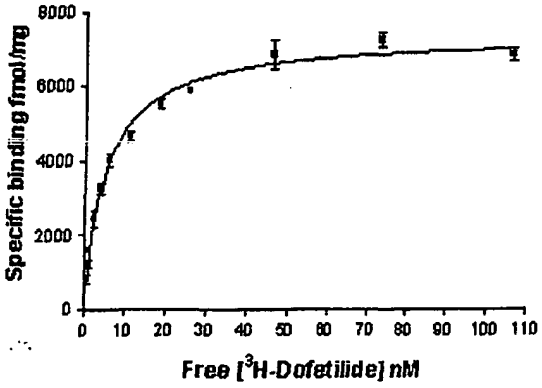
(e) comparison of the IC_{20} value of the test compound or mixture of test compounds with the concentration required for the desired therapeutic effect of the compound in vivo.

16. An assay according to any one of the preceding claims wherein the assay is performed as a filter binding assay.

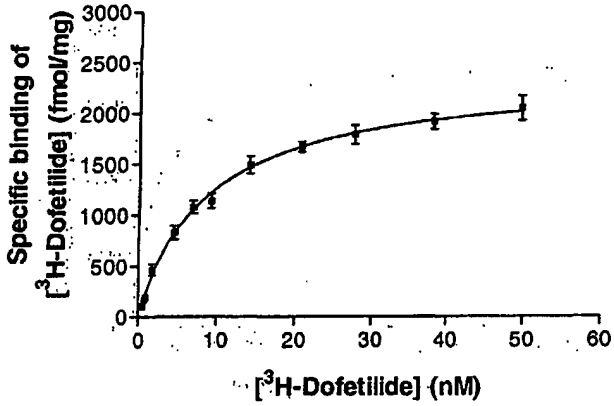
17. An assay according to any one of claims 1 to 15 wherein the assay is performed as a scintillation proximity assay.

Figure1

(a)



(b)



(c)

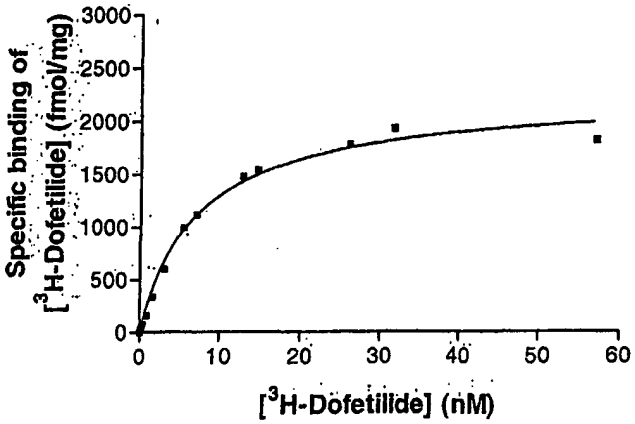
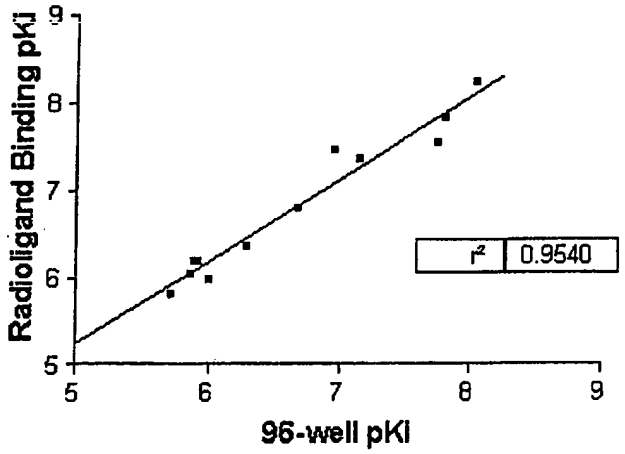


Figure 2

(a)


Radioligand Binding pKi
96-well pKi
r² 0.9540
5
6
7
8
9

(b)

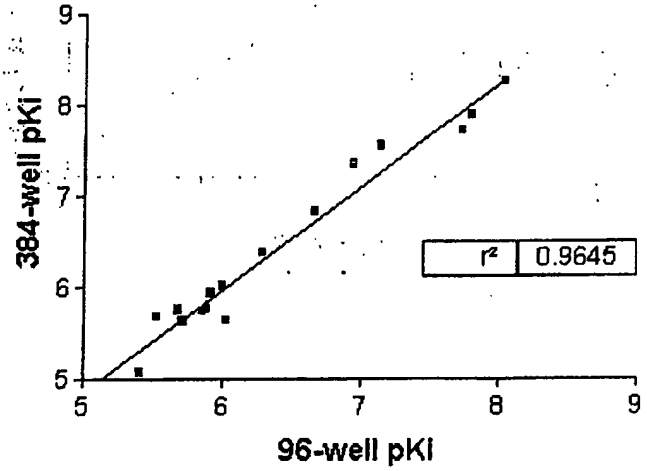
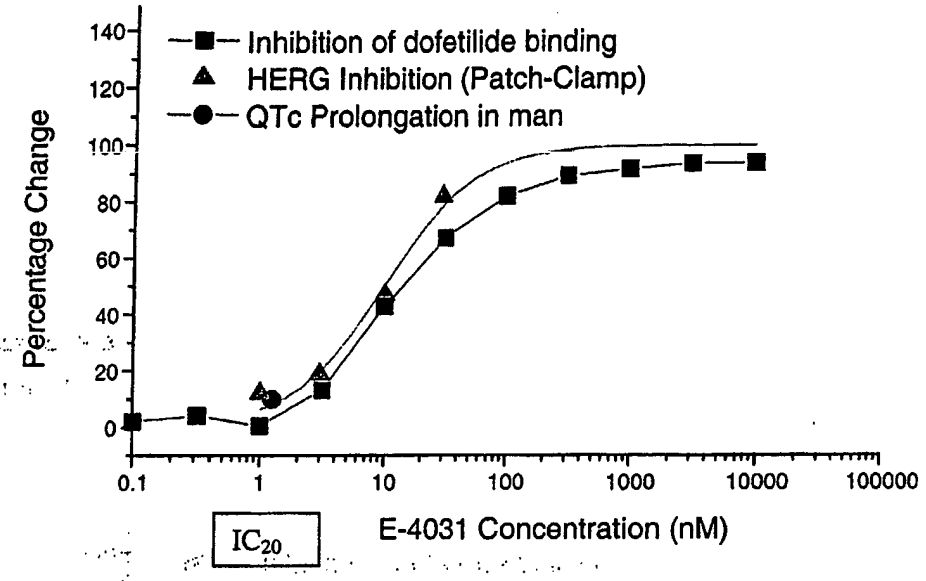

384-well pKi
96-well pKi
r² 0.9645
5
6
7
8
9

Figure 3

(a)



(b)

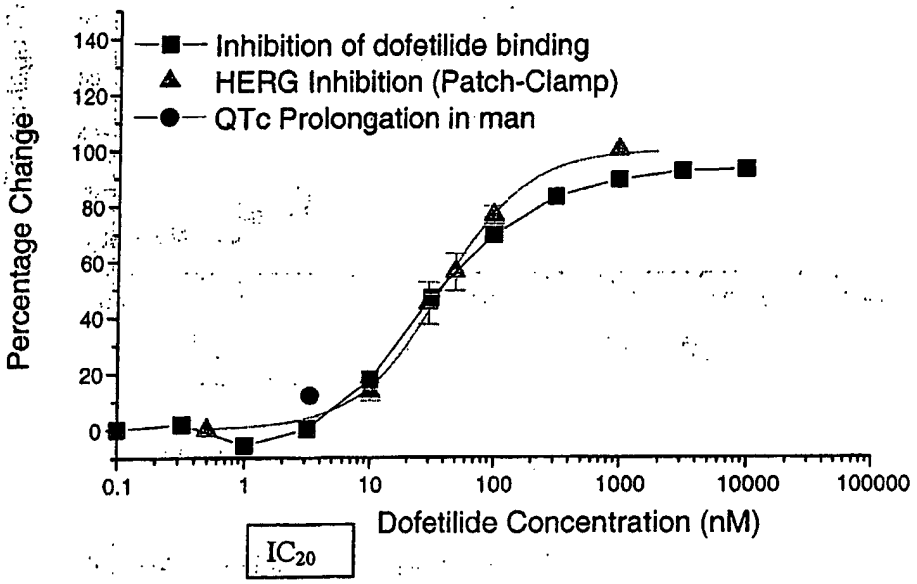
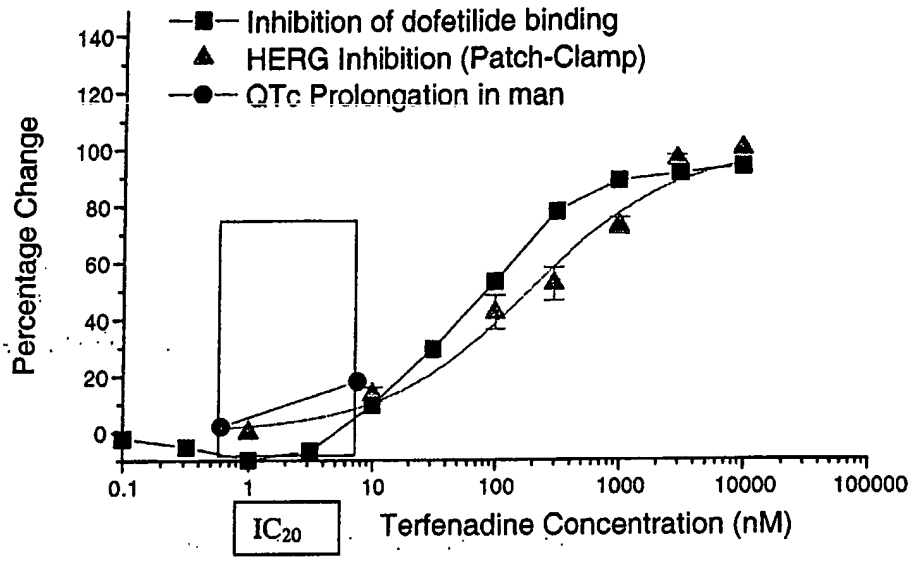


Figure 3 continued

(c)



(d)

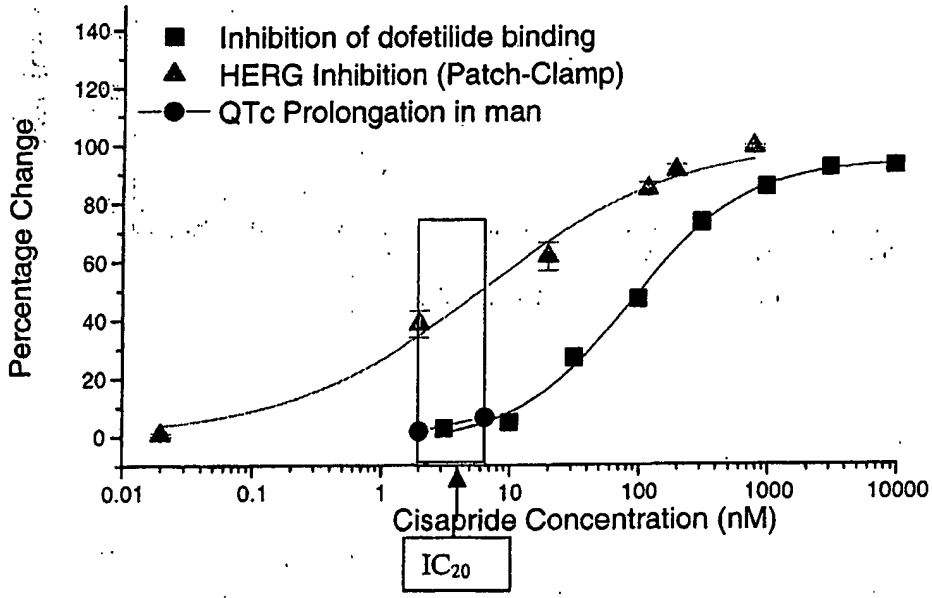


Figure 4

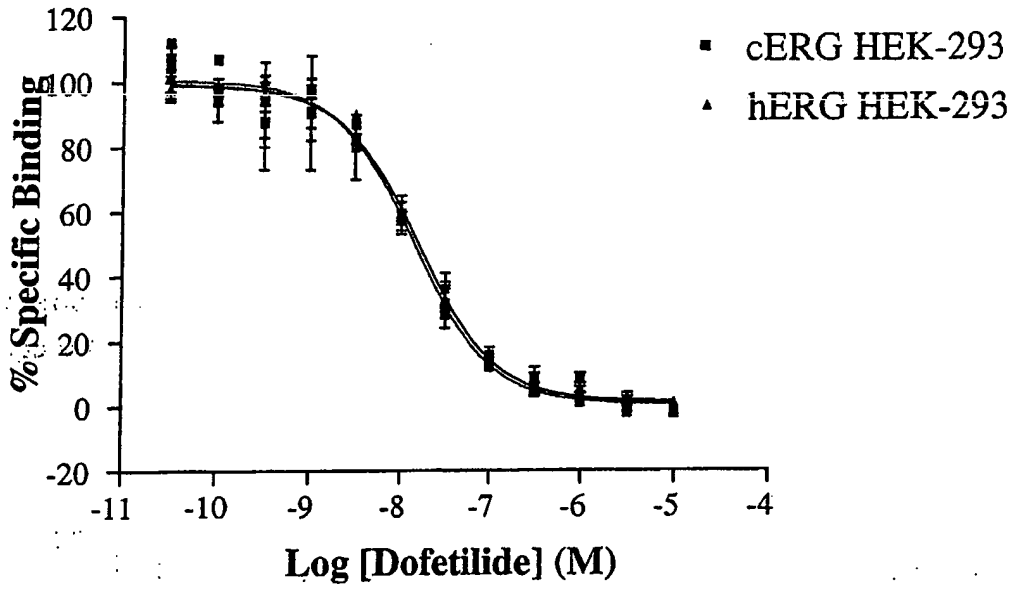


Figure 5

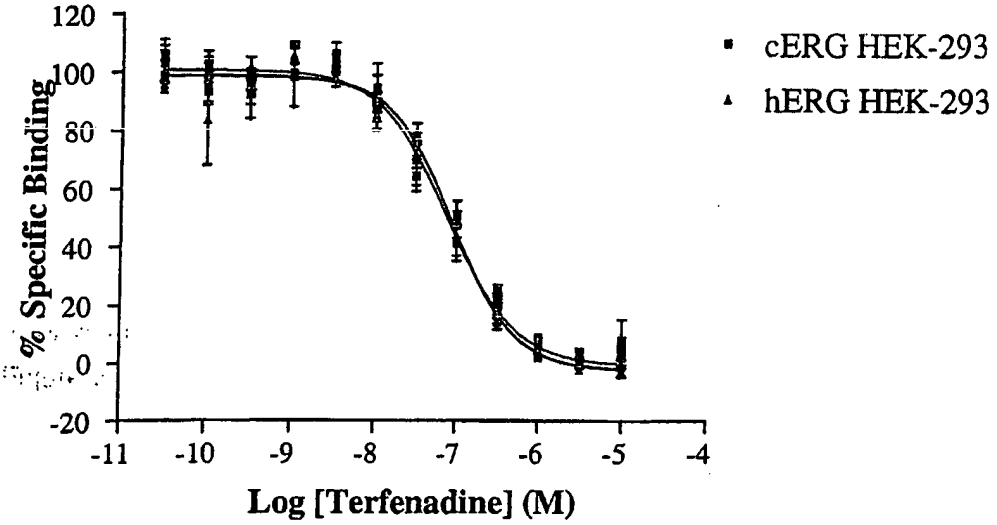

120
100
80
60
40
20
0
-20
% Specific Binding
-11
-10
-9
-8
-7
-6
-5
-4
Log [Terfenadine] (M)
cERG HEK-293
hERG HEK-293

Figure 6

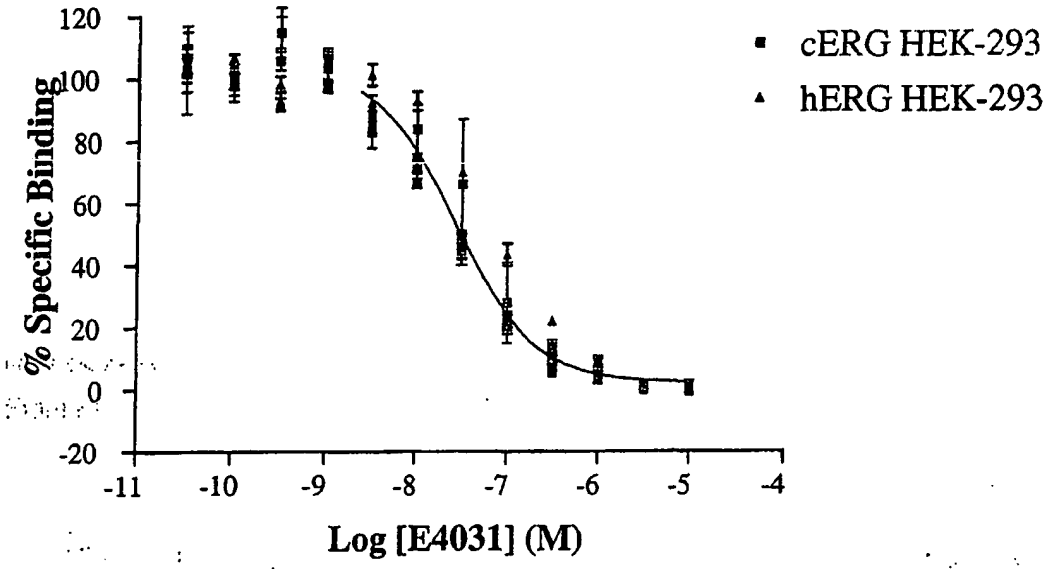
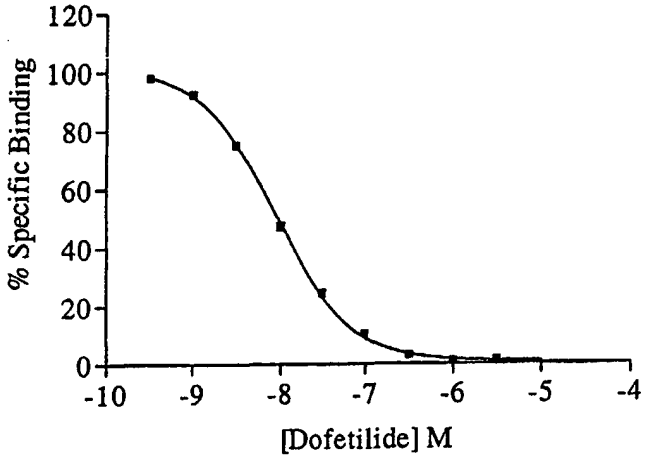
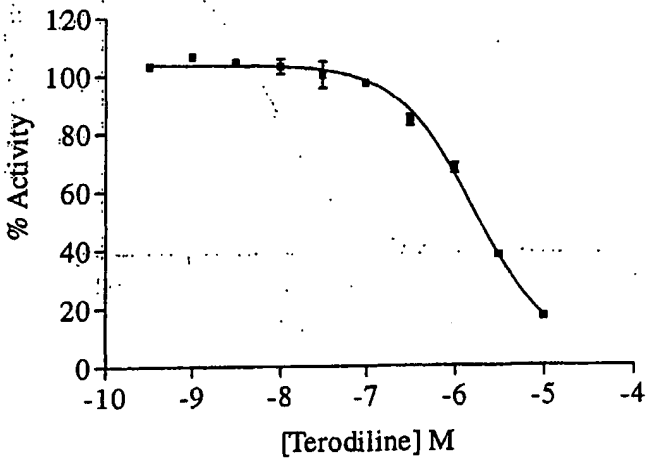


Figure 7

(a)



(b)



PCS22042 SEQUENCE LISTING

<110> Pfizer Inc (CA, EP except EP(GB), JP, US.) Pfizer Ltd (EP(GB)).

<120> Assay

<130> PCS 22042

<150> GB 0121440.2
<151> 2001-09-04

<150> US 60/323973
<151> 2001-09-20

<160> 3

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 20
<212> DNA
<213> Canine

<400> 1
accacatcca ccaggcacag 20

<210> 2
<211> 25
<212> DNA
<213> pcDNA3.1(-) vector

<400> 2
cccaagctgg ctagcgttta aacgg 25

<210> 3
<211> 23
<212> DNA
<213> pSP73 vector

<400> 3
taatacgact cactataggg aga 23

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/021271 A3

(51) International Patent Classification[7]: G01N 33/566, 33/50, 33/68

(21) International Application Number: PCT/IB02/03618

(22) International Filing Date:
4 September 2002 (04.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0121440.2 4 September 2001 (04.09.2001) GB
60/323,973 20 September 2001 (20.09.2001) US

(71) Applicant *(for GB only)*: **PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB, US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GREENGRASS, Pamela, May** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **STEWART, Michael** [GB/GB]; Pfizer Limited, U.K. Patent Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **WOOD, Claire, Margaret** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

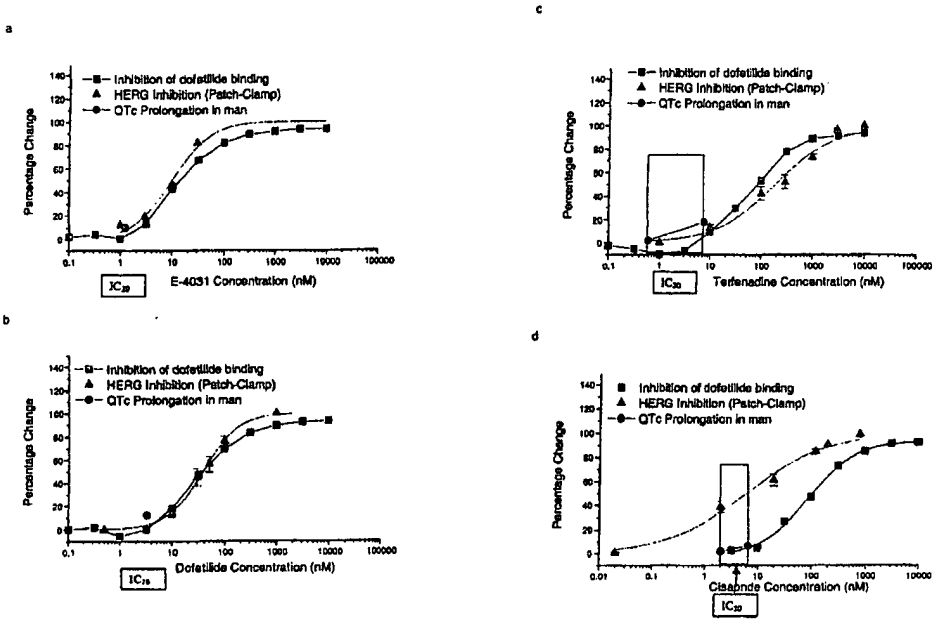
(74) Agents: **HAYLES, James, R.** et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,

[Continued on next page]

(54) Title: AFFINITY-ASSAY FOR THE HUMAN ERG POTASSIUM CHANNEL



(57) Abstract: The invention relates to an assay to establish the affinity of compounds at the "ether-a-go-go" (ERG) potassium (K+) channel, in particular the human ERG (hERG) potassium channel, using a labelled inwardly rectifying potassium channel (IKR) blocker. This assay is useful to identify compounds with undesirable effects on cardiac repolarisation in man, in particular the propensity to prolong the QT interval in the electrocardiogram.

WO 03/021271 A3

TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
18 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/03618

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/566 G01N33/50 G01N33/68

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 G01N

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, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NETZER RAINER ET AL: "Screening lead compounds for QT interval prolongation" DRUG DISCOVERY TODAY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 2, January 2001 (2001-01), pages 78-84, XP002198162 ISSN: 1359-6446	1,9-17
Y	abstract page 78, right-hand column, paragraph 2 -page 79, left-hand column, line 3 page 79, right-hand column, last paragraph -page 80, left-hand column, paragraph 1 page 81, right-hand column, last paragraph -page 82, left-hand column, paragraph 1; table 3	2-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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" 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 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
30 September 2003	13/10/2003

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	Luis Alves, D

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FINLAYSON KEITH ET AL: "dofetilide binding in SHSY5Y and HEK293 cells expressing a HERG-like K+ channel?" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 412, no. 3, 2001, pages 203-212, XP001155254 ISSN: 0014-2999 abstract page 204, left-hand column, last paragraph -right-hand column, paragraph 1 page 206, left-hand column, last paragraph -page 207, left-hand column, paragraph 1	2-8
P,X	FINLAYSON KEITH ET AL: "'3H!Dofetilide binding to HERG transfected membranes: A potential high throughput preclinical screen" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 430, no. 1, 26 October 2001 (2001-10-26), pages 147-148, XP002198164 ISSN: 0014-2999	1,9-17
Y	the whole document	2-8
P,X	WO 02 05860 A (CONNOLLY THOMAS M ;KOSTURA MATTHEW J (US); DEAN DENNIS C (US); BUT) 24 January 2002 (2002-01-24) example 3	1-17
A	CAVERO I ET AL: "DRUGS THAT PROLONG QT INTERVAL AS AN UNWANTED EFFECT: ASSESSING THEIR LIKELIHOOD OF INDUCING HAZARDOUS CARDIAC DYSRHYTHMIAS" EXPERT OPINION ON PHARMACOTHERAPY, ASHLEY, LONDON,, GB, vol. 1, no. 5, July 2000 (2000-07), pages 947-973, XP008022068 ISSN: 1465-6566 abstract page 964, right-hand column, last paragraph -page 966, left-hand column, paragraph 3	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 02/03618

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0205860 A	24-01-2002	AU 7786301 A	30-01-2002
		CA 2415295 A1	24-01-2002
		EP 1311300 A1	21-05-2003
		WO 0205860 A1	24-01-2002
		US 2002034730 A1	21-03-2002

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

JOSEPH A. COPPOLA, ESQ.
KENYON & KENYON
ONE BROADWAY
NEW YORK, NEW YORK 10004

COPY MAILED

SEP 01 2005

OFFICE OF PETITIONS

In re Application of :
Claus Meese et al :
Application No. 10/766,263 : DECISION GRANTING PETITION
Filed: January 27, 2004 : UNDER 37 CFR 1.313(c)(2)
Attorney Docket No. 12961/46102 :

This is a decision on the petition, filed August 23, 2005, under 37 CFR 1.313(c)(2) to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED**.

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid on August 15, 2005 (certificate of mailing date of August 10, 2005) in the above-identified application cannot be refunded. If, however, the above-identified application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.[1]

Telephone inquiries should be directed to the undersigned at (571) 272-3218.

This matter is being referred to Technology Center AU 1624 for processing of the request for continued examination under 37 CFR 1.114 and for consideration of the Information Disclosure Statement.

Frances Hicks
Petitions Examiner
Office of Petitions

---

[1] *The request to apply the issue fee to the new Notice may be satisfied by completing and returning the new Issue Fee Transmittal Form PTOL-85(b), which includes the following language thereon: "Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or re-apply any previously paid issue fee to the application identified above." Petitioner is advised that, whether a fee is indicated as being due or not, the Issue Fee Transmittal Form* ***must*** *be completed and timely submitted to avoid abandonment. Note the language in bold text on the first page of the Notice of Allowance and Fee(s) Due (PTOL-85).*

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/766,263	01/27/2004	Claus Meese	12961/46102

CONFIRMATION NO. 3433

OC000000016926805

26646
KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

Date Mailed: 09/01/2005

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/15/2005.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Frances Hicks

FRANCES M HICKS
OP (571) 272-3218

OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/766,263	01/27/2004	Claus Meese	55647-C (45107)

CONFIRMATION NO. 3433

OC000000016926476

21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

Date Mailed: 09/01/2005

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/15/2005.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Frances Hicks

FRANCES M HICKS
OP (571) 272-3218

OFFICE COPY

10/766,263 "EAST" UPDATED SEARCH INCLUDING INTERFERENCE SEARCH

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("2556636").PN.	USPAT	OR	OFF	2005/09/02 11:42
L2	1	("2567245").PN.	USPAT	OR	OFF	2005/09/02 11:43
L3	1	("2676964").PN.	USPAT	OR	OFF	2005/09/02 11:43
L4	1	("3261841").PN.	USPAT	OR	OFF	2005/09/02 12:42
L5	1166	514/548 OR 514/648 OR 564/316 OR 560/194	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2005/09/02 12:43
L6	47	L5 AND (MUSCARINIC OR TOLTERODINE)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2005/09/02 12:44

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26646 7590 09/09/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/09/2005

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	12961/46102	3433

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$0	$0	$0	12/09/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 07/05) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

or Fax **(571) 273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26646 7590 09/09/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	12961/46102	3433

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$0	$0	$0	12/09/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-548000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,263	01/27/2004	Claus Meese	12961/46102	3433

26646 7590 09/09/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/09/2005

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 07/05) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *RCE 23 August 2005*.

2. ☒ The allowed claim(s) is/are *50-63*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *09/700,094* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 23Aug05
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The following amendments to the specification are necessary to render the instant application compliant with 37 CFR 1.77 (arrangement and contents of the specification) and 37 CFR 1.78(a)(1)(iv)(i) (cross-reference to related applications), and reflect the arrangement and contents of the specification of the parent application, 09/700,094. Applicants' preliminary amendment filed 27 January 2004 included a cross-reference to the parent application, serial number 09/700,094, but that application had not yet issued as a patent. The cross-reference to the parent application is re-stated hereinbelow, with added reference to the patent number of the parent application.

IN THE SPECIFICATION –

At page 1, under the title of the application, insert the following paragraph:

"The present application is a Continuation Application of USSN 09/700,094, filed January 2, 2001, now US Patent 6,713,464, which in turn claimed the priority benefit of PCT/EP99/03212, filed May 11, 1999."

Followed by the heading:

--BACKGROUND OF THE INVENTION--

At page 3, line 17 (before the paragraph that begins "It is an object...") insert the heading:

--SUMMARY OF THE INVENTION--

At page 4, starting at line 4 (BEFORE the paragraph beginning that begins "According to the present invention..." insert the following paragraph and headings:

--BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** shows the formation of the active metabolite from different prodrugs by human liver S 9(%) in 1 hour.

DETAILED DESCRIPTION OF THE INVENTION--

end of amendments

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after allowance. Since this application is eligible for continued examination under 37 C.F.R.1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 C.F.R. 1.114. Applicant's submission filed on 23 August 2005 has been entered and considered by the examiner, and forms PTO-1449 initialed and signed by the examiner, to that effect are enclosed herewith.

Allowable Subject Matter

Claims 50-63 are allowed.

The reasons for indication of allowable subject matter remain the same as were explained in the Notice of Allowability mailed 10 May 2005, and can be found in that Office action.

The submission of the Information Disclosure Statement of 23 August 2005, with the Requested for Continued Examination under 37 C.F.R. 1.114 has been considered and none of the cited references are novelty-destroying or render obvious the claimed compounds, methods and compositions.

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-872-9306, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312;

information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

zt

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	ATTY. DOCKET NO. 12961/46102	APPLICATION NO. 10/766,263
Form PTO-1449	APPLICANT Claus MEESE et al.	
	FILING DATE January 27, 2004	GROUP 1624

U. S. PATENT DOCUMENTS*

EXAMINER INITIAL	PATENT/PUBLICATION NUMBER	PATENT/PUBLICATION DATE	NAME	CLASS	SUBCLASS	FILING DATE*
ZT	2,556,636	June 12, 1951	Nathan Sperber et al.	260	247.1	
ZT	2,567,245	September 11, 1951	Nathan Sperber et al.	260	296	
ZT	2,676,964	April 27, 1954	Nathan Sperber et al.	260	256.4	
ZT	3,261,841	July 19, 1966	Bernard L. Zenitz	260	292	

*- copies of U.S. references are not enclosed

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
ZT	830,193	February 04, 1952	DE	—	—	X	
ZT	685 696	January 07, 1953	GB	—	—		
ZT	689 835	April 08, 1953	GB	—	—		
ZT	690 274	April 15, 1953	GB	—	—		
ZT	692 931	June 17, 1953	GB	—	—		
ZT	1 169 944	November 05, 1969	GB	—	—		
ZT	1 169 945	November 05, 1969	GB	—	—		
ZT	WO 03/021271	March 13, 2003	PCT	—	—		

OTHER DOCUMENTS

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
ZT		Abstracts from the 26th Annual Meeting of the International Incontinence Society, August 27-30, 1996, Gillberg et al., abstract 33, Neurology and Urodynamics 15:308-309
ZT		Andersson & Hedlund, "Pharmacological perspective on the physiology of the lower urinay tract," 2002, Urology 60(Suppl. 5A):13-20
ZT		Committee for Proprietary Medicinal Products, "The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products," CPMP/986/96, December 17, 1997
ZT		Gardner & Altman, "Confidence intervals rather than P values: estimation rather than hypothesis testing," 1986, Br. Med. J. 292:746-750
ZT		Kang et al., "Cardiac ion channel effects of Tolterodine," 2004, J. Pharmacol. Exper. Thera. 308:935-940
ZT		Klosa, "Eine Neue Synthesemethode der Darstellung von Diarylalkylaminen," 1966, Journal für Praktische Chemie 4:312-334 (in German) with English translation

EXAMINER _____ DATE 2 SEPTEMBER 2005

APPLICATION NO. 10/766,263

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
ET		Lipinsky et al., "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," 1997, Adv. Drug Deliv. Rev. 23:3-25
ET		Netzer et al., "Screening lead compounds for QT interval prolongation," 2001, Drug Discovery Today 6:78-84
ET		Nilvebrant et al., "Differences between binding affinities of some antimuscarinic drugs in the parotid gland an those in the urinary bladder and ileum," 1983, Acta Pharmacol. et Toxicol. 53 :304-313
ET		Pharmacology/Toxicology Review from Application Number 21-518, Center for Drug Evaluation and Research, pages 1-3 (2004)
ET		Roy et al., "HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine," 1996, 94:817-823

EXAMINER	DATE CONSIDERED
	2 SEPTEMBER 2005

EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/766,263	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

ISSUE CLASSIFICATION

ORIGINAL					CROSS REFERENCE(S)						
CLASS		SUBCLASS			CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
514		548			514	648						
INTERNATIONAL CLASSIFICATION					560	194						
A	01	N	37	102	564	316						
A	01	N	37	106								
A	61	K	31	225								
C	07	C	69	34								
C	07	C	211	00								

(ZACHARY C. TUCKER) 2 SEPTEMBER '05
(Assistant Examiner) (Date)

9/6/05
(Legal Instruments Examiner) (Date)

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
(Primary Examiner) (Date)

Total Claims Allowed: 14

O.G. Print Claim(s)	O.G. Print Fig.
1 (50)	1

RCE

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11		41		71		101		131		161		191
	12		42		72		102		132		162		192
	13		43		73		103		133		163		193
	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
	17		47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
	23		53		83		113		143		173		203
	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/766,263	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim Final	Claim Original	Date
	1	9/2005
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	
	14	
	15	
	16	
	17	
	18	
	19	
	20	
	21	
	22	
	23	
	24	
	25	
	26	
	27	
	28	
	29	
	30	
	31	
	32	
	33	
	34	
	35	
	36	
	37	
	38	
	39	
	40	
	41	
	42	
	43	
	44	
	45	
	46	
	47	
	48	
	49	
1	50	=

Claim Final	Claim Original	Date
	2	9/2005
	3	11
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	↓
	14	=
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

Claim Final	Claim Original	Date
	101	
	102	
	103	
	104	
	105	
	106	
	107	
	108	
	109	
	110	
	111	
	112	
	113	
	114	
	115	
	116	
	117	
	118	
	119	
	120	
	121	
	122	
	123	
	124	
	125	
	126	
	127	
	128	
	129	
	130	
	131	
	132	
	133	
	134	
	135	
	136	
	137	
	138	
	139	
	140	
	141	
	142	
	143	
	144	
	145	
	146	
	147	
	148	
	149	
	150	

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/766,263	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

- RCE- UPDATE -

SEARCHED

Class	Subclass	Date	Examiner
560	194	9/2/05 REVIEWED SEARCH.	ZT
564	316		
514	548		
	648		

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
PALM - REVIEW OF INVENTOR NAMES SEARCH		
EAST - REVIEW OF UPDATED SEARCH OF 4/20/05	9/2/05	ZT
STN - SEARCH TRANSCRIPT FROM 4/20/05 WAS REVIEWED		

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner
EAST - USPPG-PUB			
514	548, 648	9/2/05 CROSS-REFERENCED W/ "MUSCARINIC" OR "TOLTERODINE"	ZT
560	194		
564	316		

(SEARCH HISTORY ATTACHED)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 34

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKE NO.
10/766,263	01/27/2004 RULE	514	1624	55647-C (45107)

APPLICANTS

Claus Meese, Monheim, GERMANY;

Bengt Sparf, Trangsund, SWEDEN;

** CONTINUING DATA **********

This application is a CON of 09/700,094 01/02/2001 PAT 6,713,464 which is a 371 of PCT/EP99/03212 05/11/1999

** FOREIGN APPLICATIONS **********

EUROPEAN PATENT OFFICE (EPO) 98108608.5 05/12/1998

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 06/16/2004

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDE
35 USC 119 (a-d) conditions met	COUNTRY	DRAWING	CLAIMS	CLAIMS
Verified and Acknowledged	GERMANY	1	22	4

☒ yes ☐ no
☒ yes ☐ no ☐ Met after Allowance
Examiner's Signature
Initials

ADDRESS
21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON , MA
02205

TITLE
Novel derivatives of 3,3-diphenylpropylamines

FILING FEE	FEES: Authority has been given in Paper	☐ All Fees
RECEIVED	No. _____ to charge/credit DEPOSIT ACCOUNT	☐ 1.16 Fees (Filing)
2262	No. _____ for following:	☐ 1.17 Fees (Processing Ext. of time
		☐ 1.18 Fees (Issue)
		☐ Other _____

h e e e e e c

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

REQUEST FOR CONTINUED EXAMINATION (RCE)
TRANSMITTAL FORM (37 C.F.R. § 1.114)

DOCKET NO.	APPLICATION SERIAL NO.	EXAMINER	ART UNIT
12961/46102	**10/766,263**	**Zachary C. TUCKER**	**1624**

INVENTOR(S): **Claus MEESE et al.**

Address to:

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: December 8, 2005

Signature: Chandra Seeranen

This is a **request for continued examination** under 37 C.F.R. § 1.114 (RCE) of pending application Serial No. **10/766,263**, filed on **January 27, 2004**, entitled **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES.**

The following constitute the submission **required** by 37 C.F.R. § 1.114(a) and is attached:

_____ Amendment
__X__ Information Disclosure Statement and Form PTO-1449
_____ Drawing Changes
_____ Other Submission: _____

1. The filing fee for this RCE and the required amendment/submission is calculated below. The fee below is calculated based on the status of the claims after the entry of the attached amendment/submission. The fee for any new additional claims is included with this RCE, the fee for previously entered additional claims having already been paid.

	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT NUMBER EXTRA*	RATE ($) PER CLAIM	FEE ($)
BASIC FEE						790.00
TOTAL CLAIMS	14		89	0	x $50.00	0.00
INDEPENDENT CLAIMS	4		5	0	x $200.00	0.00
MULTIPLE DEPENDENT CLAIM	1		1	0	$360.00	0.00
				*Number extra must be zero or larger	TOTAL	**790.00**
	If Applicant is a small entity under 37 C.F.R. §§ 1.9 and 1.27, then divide total fee by 2, and enter amount here.				SMALL ENTITY TOTAL	

2. Please charge the required RCE and submission filing fee of **$790.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11–0600**.

3. The Commissioner is hereby authorized to charge payment of the fees, including any additional fees required, associated with this communication or arising during the pendency of this application, or to credit any overpayment, to the deposit account of **Kenyon & Kenyon**, deposit account number **11–0600**.

4. A duplicate of this transmittal form is enclosed.

Dated: DECEMBER 8, 2005

By: Respectfully submitted,

Joseph A. Coppola

Joseph A. Coppola (Reg. No. 38,413)
KENYON & KENYON
One Broadway
New York, New York 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NO. 26646

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
INFORMATION DISCLOSURE STATEMENT		Docket Number: **12961/46102**	
Application Number **10/766,263**	Filing Date **January 27, 2004**	Examiner **Z. C. TUCKER**	Art Unit **1624**
Invention Title **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor **Claus MEESE et al.**	

Address to:

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 35 U.S.C. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorneys for Applicant hereby brings the following references to the attention of the Examiner. These references are listed on the attached modified PTO Form No. 1449. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. The filing of this Information Disclosure Statement and the enclosed PTO 1449 shall not be construed as an admission that the information cited is prior art, or is considered to be material to patentability as defined in 37 C.F.R. §1.56(b).

3. A copy of each patent, publication or other information listed on the modified PTO 1449 is enclosed, unless otherwise noted.

4. It is believed that no fees are due in connection with this Information Disclosure Statement. However, should any fees be due, the Commissioner is authorized to charge Deposit Account No. 11-0600 for such fees. A duplicate of this communication is enclosed for charging purposes.

Dated: DECEMBER 8, 2005

By: Joseph A Coppola

Joseph A. Coppola (Reg. No. 38,413)
KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NUMBER 26646

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop RCE
Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on

Date: December 8, 2005

Signature: Chandra Serrano

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449	ATTY. DOCKET NO. 12961/46102	APPLICATION NO. 10/766,263
	APPLICANT Z.C. TUCKER	
	FILING DATE January 27, 2004	GROUP 1624

U. S. PATENT DOCUMENTS*

EXAMINER INITIAL	PATENT/PUBLICATION NUMBER	PATENT/PUBLICATION DATE	NAME	CLASS	SUBCLASS	FILING DATE*
	3,446,901	May 27, 1969	G. J. Macclesfield			
	4,988,730	January 29, 1991	Korbonits et al.			
	5,382,600	January 17, 1995	Jonsson et al.			
	5,559,269	September 24, 1996	Johansson et al.			
	5,922,914	July 13, 1999	Gage et al.			
	6,517,864	February 11, 2003	Orup Jacobsen et al.			
	6,630,162	October 7, 2003	Nilvebrant et al.			
	6,713,464	March 30, 2004	Meese et al.			
	6,770,295	August 3, 2004	Kreilgard et al.			
	6,783,769	August 31, 2004	Arth et al.			
	6,809,214	October 26, 2004	Meese			
	6,809,225	October 26, 2004	Donsbach et al.			
	6,858,650	February 22, 2005	Meese			
	6,890,920	May 10, 2005	Richards et al.			
	6,911,217	June 28, 2005	Gren et al.			
	2003/0124179	July 3, 2003	Jacobsen, Lene O. et al.			
	2004/0186061	September 23, 2004	Meese, Claus et al.			
	2005/0004223	January 6, 2005	Slatter, John G. et al.			

*- copies of U.S. references are not enclosed

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
	925 468 (in German, with English translation)	March 21, 1955	DE			YES	
	1 216 318 (in German, with English translation)	May 12, 1966	DE			YES	
	325 571	July 26, 1989	EP				
	667 852	August 23, 1995	EP				
	1 019 358	July 19, 2000	EP				
	1 077 912	February 28, 2001	EP				
	1 128 819	September 05, 2001	EP				
	624 117	May 27, 1949	GB				
	627 139	July 29, 1949	GB				
	WO 93/23025	November 25, 1993	PCT				
	WO 96/12477	May 02, 1996	PCT				

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
	WO 98/03067	January 29, 1998	PCT				
	WO 00/12069	March 09, 2000	PCT				
	WO 00/27364	May 18, 2000	PCT				
	WO 01/34139	May 17, 2001	PCT				

OTHER DOCUMENTS

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Abrams et al., "Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder," 1998, Br. J. Urol. 81:801-810
		Anderson et al., "Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence," 1999, J. Urol. 161:1809-1812
		Andersson et al., "Pharmacological treatment of urinary incontinence," in Abrams P., Khoury S., Wein A. (Eds), Incontinence, 2nd International Consultation on Incontinence, Plymouth, Plymbridge Distributors Ltd, UK, Plymouth, 2002, pp 479-511
		Andersson, "Antimuscarinics for treatment of overactive bladder," 2004, Lancet Neurol. 3:46-53
		Andersson & Wein, "Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence," 2004, Pharmacol. Rev. 56:581-631
		Appell et al., "Prospective randomized controlled trial of extended release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT study," 2001, Mayo Clinic Proceedings 76:358-363
		Breidenbach et al., "Pharmacodynamic profiling of the novel antimuscarinic drug fesoterodine on rat bladder," 2002, Proceedings of the International Continence Society, 32:449
		Brynne et al., "Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine, 1998, Clin. Pharmacol. Thera. 63:529-539
		Brynne et al., "Tolterodine does not affect the human in vivo metabolism of the probe drugs caffeine, debrisoquine, and omeprazole," 1999, Br. J. Clin. Pharmacol. 47:145-150
		Brynne et al., "Fluoxetine inhibits the metabolism of tolterodine – pharmacokinetic implications and proposed clinical relevance," 1999, Br. J. Clin. Pharmacol. 48:553-563
		Brynne et al., "Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity," 1999, Br. J. Clin. Pharmacol. 48:564-572
		Cawello et al., "Multiple dose pharmacokinetics of fesoterodine in human subjects," 2002, Nauyn-Schmiedeberg's Arch. Pharmacol. 365 (Suppl. 1):428, 2002
		Chancellor et al., "A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate," 2001, Clinical Therapeutics 23:753-760
		Chapple & Udo, "Delay to maximum effect in overactive bladder patients treated with oxybutynin or tolterodine," 2000, European Urology 37(Suppl. 2):84, abstract 335 from the XVth Congress of the European Association of Urology, Brussels, Belgium, April 12-15, 2000
		Chapple et al., "Fesoterodine a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome: results of a Phase II controlled study," 2004, Proceedings of the International Continence Society, 34:142
		Clemett & Jarvis, "Tolterodine: a review of its use in the treatment of overactive bladder," 2001, Drugs & Aging 18:277-304
		Cole, "Fesoterodine, an advanced antimuscarinic for the treatment of overactive bladder: A safety update," 2004, Drugs of the Future 29:715-720
		Detrol® package insert, Pharmacia & Upjohn Co., April, 2004
		Diokno et al., "Tolterodine (Detrol®) improves incontinence and nocturia in urological based study," 1999 April, J. Urol. 161 (4 Suppl):256, abstract 987

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Ekstrom et al., "Effects of tolterodine on bladder function in healthy volunteers," Journal of Urology 153(Suppl.):394A, abstract 662 from the 19th Annual Meeting of the American Urological Association, Las Vegas, April 23-28, 1995
		Gillberg et al., "Tolterodine, a new agent with tissue effect selectivity for urinary bladder," 1994, Neurourology and Urodynamics 13:435-436, abstract 60B from International Continence Society 24th Annual Meeting, Prague, Czech Republic, August 1994
		Gillberg et al., "Comparison of the in vitro and in vivo profiles of tolterodine with those of subtype-selective muscarinic receptor antagonists," 1998, European Journal of Pharmacology 349: 285-292
		Hills et al., "Tolterodine," 1998, Drugs 55:813-820
		Jonas et al., "Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation," 1997, World J. Urol. 15:144-151
		Kershen & Hsieh, "Preview of new drugs for overactive bladder and incontinence: darifenacin, solifenacin, trospium, and duloxetine," Curr. Urol. Rep. 5:359-367
		Klosa, "Eine Neue Synthese von Diphenylisopropylaminen," 1966, Journal für Praktische Chemie 4:335-340 (in German, with English translation)
		Larsson et al., "Tolterodine in the treatment of overactive bladder: analysis of the pooled phase II safety and efficacy data," 1999, Urology 53: 990-998
		Millard et al., "Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity," 1999, J. Urol. 161:1551-1555
		Modiri et al., "Effect of muscarinic antagonists on micturition pressure measured by cystometry in normal, conscious rats," 2002, Urology 59:963-968
		Naerger et al., "Effect of tolterodine on electrically induced contractions of isolated human detrusor muscle from stable and unstable bladders," 1995, Neurourology and Urodynamics 14:524-526, abstract 76 from International Continence Society 25th Annual Meeting, Sydney, Australia, October 1995
		Nilsson et al., "Comparison of a 10 mg controlled release oxybutynin tablet with a 5 mg oxybutynin tablet in urge incontinence patients," 1997, Neurourol. Urodyn. 16:533-542
		Nilvebrant & Sparf, "Receptor binding profiles of some selective muscarinic antagonists," 1988, European Journal of Pharmacology 151:83-96
		Nilvebrant et al., "The in vitro pharmacological profile of tolterodine – a new agent for the treatment of urinary urge incontinence," 1994, Neurourology and Urodynamics 13:433-435, abstract 60A from International Continence Society 24th Annual Meeting, Prague, Czech Republic, August 1994
		Nilvebrant et al., "Tolterodine is not subtype (m1-m5) selective but exhibits functional bladder selectivity in vivo," 1996, Neurourology and Urodynamics 15:310-311, abstract 34 from the 26th Annual Meeting of the International Continence Society, Athens, Greece, August 27-30, 1996
		Nilvebrant, "Tolterodine and terodiline – different pharmacological profiles," pages 141-142, abstract 181a, from the 27th Annual meeting of the International Continence Society, Yokohama, Japan, September 1997
		Nilvebrant et al "Tissue distribution of tolterodine and its metabolites: low penetration into the central nervous system," 2000, European Urology 37(Suppl. 2):84, abstract 333 from the XVth Congress of the European Association of Urology, Brussels, Belgium, April 12-15, 2000
		Nilvebrant, "The mechanism of action of tolterodine," 2000, Reviews in Contemporary Pharmacotherapy 11:13-27
		Olsson et al., "Food increases the bioavailability of tolterodine but not effective exposure," 2001, J. Clin. Pharmacol. 41:298-304
		Olsson & Szamosi, "Food does not influence the pharmacokinetics of a new extended release formulation of tolterodine for once daily treatment of patients with overactive bladder," 2001, Clinical Pharmacokinetics 40:135-143
		Olsson & Szamosi, "Multiple dose pharmacokinetics of a new once daily extended release formulation versus immediate release tolterodine," 2001, Clinical Pharmacokinetics 40:227-235

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Rentzhog et al., "Efficacy and safety of tolterodine in patients with detrusor instability: a dose ranging study," 1998, Br. J. Urol. 81:42-48
		Sachse et al., "Pharmacodynamics of multiple dose treatment with the novel antimuscarinic drug fesoterodine," 2002, Nauyn-Schmiedeberg's Arch. Pharmacol. 365 (Suppl. 1):413
		Sachse et al., "Safety and pharmacokinetics of the novel bladder-selective antimuscarinic drug fesoterodine in populations of different age or gender," 2002, Proceedings of the International Continence Society, 32:441
		Sachse et al., "Safety and pharmacokinetics of the novel bladder-selective antimuscarinic fesoterodine in populations of different ethnic origin," 2003, Proceedings of the International Continence Society, 33:377
		Sachse et al., "Dose-proportional pharmacokinetics of the new antimuscarinic fesoterodine," 2003, Nauyn-Schmiedeberg's Arch. Pharmacol. 367 (Suppl. 1):446
		Sachse et al., "Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel, bladder-selective antimuscarinic fesoterodine," 2003, Eur. Urol. Suppl 2:111
		Sachse et al., "Concomitant food intake does not significantly influence the pharmacokinetics of the novel, bladder-selective antimuscarinic fesoterodine," 2004, Proceedings of the International Continence Society, 34:580
		Sachse et al., "Safety, tolerability and pharmacokinetics of fesoterodine in patients with hepatic impairment," 2004, Proceedings of the International Continence Society, 34:585
		Sachse et al., "Safety, tolerability and pharmacokinetics of fesoterodine after co-treatment with the potent cytochrome P450 3A4 inhibitor ketoconazole," 2004, Proceedings of the International Continence Society, 34:586
		Sachse et al., "Clinical pharmacological aspects of the novel bladder-selective antimuscarinic fesoterodine, " 2004, Progrès en Urologie, 14 (Suppl. 3):58
		Stahl et al., "Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity," 1995, Neurourol. Urodyn. 14:647-55
		Teuvo et al "Extended release tolterodine compared with immediate release tolterodine for the treatment of overactive bladder," 2000, European Urology 37(Suppl. 2):84, abstract 334 from the XVth Congress of the European Association of Urology, Brussels, Belgium, April 12-15, 2000
		Van Kerrebroeck et al., "Tolterodine once daily: superior efficacy and tolerability in the treatment of the overactive bladder," 2001, Urology 57:414-421
		Van Kerrebroeck et al., "Clinical efficacy and safety of tolterodine compared to oxybutynin in patients with overactive bladder," 1997, Neurourol. Urodyn. 16:478-479, abstract no. 91 from the 27th Annual meeting of the International Continence Society, Yokohama, Japan, September 1997
		Versi et al., "Dry mouth with conventional and controlled release oxybutynin in urinary incontinence," 2000, Obstet. Gynecol. 95:718-721
		Wefer et al., "Tolterodine: an overview," 2001, World Journal of Urology 19:312-318

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
21. MÄRZ 1955

DEUTSCHES PATENTAMT

PATENTSCHRIFT

Nr. 925 468

KLASSE 12q GRUPPE 102

F 3835 IVc / 12q

Dr. Max Bockmühl †, Bad Soden (Taunus) und
Dr. Leonhard Stein, Bad Soden (Taunus)
sind als Erfinder genannt worden

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

Verfahren zur Herstellung von γ, γ-Diaryl-propyl-aminen

Patentiert im Gebiet der Bundesrepublik Deutschland vom 13. August 1941 an
Der Zeitraum vom 8. Mai 1945 bis einschließlich 7. Mai 1950 wird auf die Patentdauer nicht angerechnet
(Ges. v. 15. 7. 51)
Patentanmeldung bekanntgemacht am 19. August 1954
Patenterteilung bekanntgemacht am 24. Februar 1955

In den Patentschriften 766 207 und 908 136 ist die Herstellung von basischen Diarylalkyl- oder Diarylcycloalkylverbindungen beschrieben, welche darin besteht, daß man Diarylmethane, deren Arylgruppen auch untereinander verbunden sein können, mit basischen Alkyl- bzw. Cycloalkylresten verknüpft bzw. daß man einen basischen Rest enthaltende Diarylessigsäureverbindungen mit den Säurerest abspaltenden Mitteln behandelt.

In der Patentschrift 875 660 ist ferner ein Verfahren beschrieben, welches dadurch gekennzeichnet ist, daß man β-tert.-Amino-propionsäureester mit Phenylmagnesiumhalogeniden zu γ-tert.-Amino-α, α-diphenylpropanolen umsetzt, aus diesen Wasser abspaltet und die Produkte hydriert.

In Weiterverfolgung dieser Arbeitsrichtung wurde nun gefunden, daß man zu den gleichen oder ähnlichen Verbindungen auch dadurch gelangen kann, daß man in β-Stellung basisch substituierte Propiophenone mit metallorganischen Aryl- bzw. Aralkylverbindungen umsetzt, die erhaltenen tertiären Carbinole durch Wasserabspaltung in die entsprechenden ungesättigten Basen überführt und letztere hydriert. Beispielsweise setzt man β-Piperidinopropiophenon mit Phenylmagnesiumbromid um und erhitzt das erhaltene Carbinol kurze Zeit mit Salzsäure auf dem Wasserbad. Man erhält dabei γ, γ-Diphenylallylpiperidin, welches durch Hydrierung in γ, γ-Diphenylpropylpiperidin übergeht.

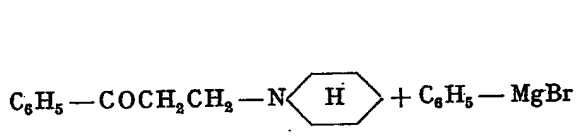
Das vorliegende Verfahren bietet gegenüber den obengenannten Verfahren den Vorteil leichterer Herstellbarkeit von Diarylpropylaminen mit untereinander verschiedenen Arylgruppen. Die bei dem vorliegenden Verfahren anfallenden Produkte haben therapeutisches Interesse und sollen daher als solche oder zur Herstellung anderer Arzneistoffe Verwendung finden.

Beispiel 1

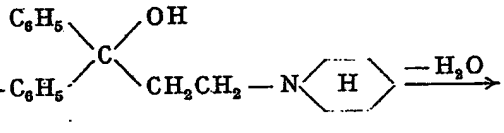
Zu einer Phenylmagnesiumbromidlösung aus 63 g Brombenzol und 9,6 g Magnesium in 200 ccm Äther werden 43 g β-Piperidinopropiophenon, gelöst in 50 ccm Äther, zutropfen gelassen. Das Ganze wird noch 4 Stunden unter Rückfluß gekocht. Alsdann gießt man die Flüssigkeit auf ein Gemisch von 500 Gewichtsteilen Eis und 100 Gewichtsteilen konzentrierter Salzsäure. Dabei scheidet sich als kristalliner Niederschlag 1,1-Diphenyl-3-piperidinopropanol-(1)-hydrochlorid ab. Die Verbindung wird abgesaugt, mit Wasser und Essigester gewaschen und aus Methanol unter Zusatz von Äther umkristallisiert. Schmelzpunkt 216 bis 217°. Zur Wasserabspaltung werden 10 g der aus dem Hydrochlorid frei gemachten Base in 30 ccm 85%iger Phosphorsäure gelöst und 1 Stunde auf 130° erhitzt. Nach dem Abkühlen der Flüssigkeit verdünnt man mit der 3- bis 4fachen Menge Wasser und macht mit starker Natronlauge alkalisch. Dabei scheidet sich das γ,γ-Diphenylallylpiperidin als Öl ab, das in Äther aufgenommen wird. Die ätherische Lösung wird mit alkoholischer Salzsäure neutralisiert, wobei sich das γ,γ-Diphenylallylpiperidinhydrochlorid abscheidet, das nach dem Umkristallisieren aus Aceton bei 204 bis 206° schmilzt.

Zwecks Überführung in die gesättigte Verbindung wird das erhaltene Hydrochlorid in Alkohol gelöst und mit Palladium und Wasserstoff hydriert. Nach Aufnahme der berechneten Menge Wasserstoff saugt man vom Katalysator ab und engt die Flüssigkeit im Vakuum ein. Der Rückstand wird aus Alkohol unter Zusatz von Äther umkristallisiert. Das 1,1-Diphenyl-3-piperidinopropan-hydrochlorid schmilzt bei 215 bis 216°. Die Umsetzung erfolgt nach folgendem Reaktionsschema:

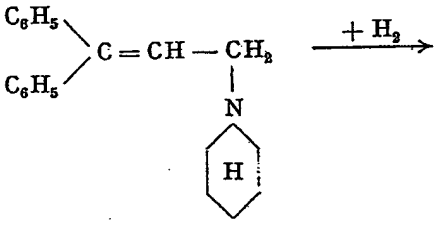
β-Piperidinopropiophenon



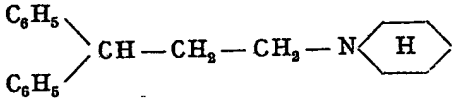
1,1-Diphenyl-3-piperidinopropanol-(1)



γ,γ-Diphenylallylpiperidin



1,1-Diphenyl-3-piperidinopropan



Beispiel 2

Zu einer Grignardlösung aus 53 g p-Bromtoluol und 7,2 g Magnesium in 300 ccm Äther werden 35 g β-Dimethylaminopropiophenon, gelöst in 50 ccm Äther, unter Kühlung zugetropft. Nach 3stündigem Kochen unter Rückfluß wird das Ganze auf Eis gegossen und die ätherische Flüssigkeit abgetrennt. Die Ätherlösung wird mit Wasser durchgewaschen, kurz über Natriumsulfat getrocknet und auf ein kleines Volumen eingeengt. Dabei kristallisiert aus der Ätherlösung 1-Phenyl-1-p-tolyl-3-dimethylamino-propanol-(1) aus, das mit Äther und Petroläther gewaschen wird. Das Hydrochlorid der Base schmilzt bei 185°.

10 g des erhaltenen 1-Phenyl-1-p-tolyl-3-dimethylamino-propanol-(1) werden in 30 ccm 85%iger Phosphorsäure gelöst und 1 Stunde auf 130 bis 135° erhitzt. Nach dem Abkühlen der Flüssigkeit verdünnt man mit Wasser und macht mit starker Natronlauge unter guter Kühlung alkalisch. Die sich dabei abscheidende Base wird in Äther aufgenommen. Die ätherische Flüssigkeit wird über Natriumsulfat getrocknet und der Äther abdestilliert. Als Ätherrückstand hinterbleibt das γ-Phenyl-γ-p-tolyl-allyl-dimethylamin in öliger Form. Die ölige Base wird in Alkohol gelöst, mit alkoholischer Salzsäure neutralisiert und mit Palladium und Wasserstoff hydriert. Nach Aufnahme der berechneten Menge Wasserstoff wird vom Katalysator abgesaugt und die alkoholische Lösung im Vakuum eingeengt. Der erhaltene Rückstand wird in heißem Essigester gelöst und filtriert. Nach kurzer Zeit kristallisiert beim Abkühlen aus der Essigesterlösung das 1-Phenyl-1-p-tolyl-3-dimethylamino-propan-hydrochlorid aus. Schmelzpunkt 156°.

Beispiel 3

50 g β-Dimethylaminopropiophenon werden in 100 ccm absolutem Äther gelöst und zu einer Grignardlösung, hergestellt aus 8,2 g Magnesiumspänen,

100 ccm absolutem Äther und 64 g p-Bromanisol, getropft. Danach wird auf Eis gegossen, die ätherische Lösung abgetrennt und letztere mit verdünnter Salzsäure durchgeschüttelt. Die saure Lösung wird mit Natronlauge alkalisch gemacht und die abgeschiedene Base in Äther aufgenommen. Der Rückstand siedet im Vakuum unter 2 mm Druck bei 200 bis 210°. Durch Lösen in wenig Hexahydrobenzol kristallisiert nach kurzer Zeit das 1-Phenyl-1-p-methoxyphenyl-3-dimethylamino-propanol-(1) in Form farbloser Kristalle vom Schmelzpunkt 118 bis 119° aus. 13,8 g der Base werden in 280 ccm 10%iger Salzsäure gelöst und auf dem Dampfbad vollständig eingedampft. Der Rückstand wird in Wasser aufgenommen, mit Kaliumcarbonat alkalisch gemacht und ausgeäthert. Die Ätherlösung wird eingedampft, mit alkoholischer Salzsäure neutralisiert und mit Palladium und Wasserstoff hydriert. Nach Aufnahme von 1,2 l Wasserstoff wird vom Katalysator abgesaugt und die alkoholische Lösung eingedampft. Aus dem Rückstand wird mit Alkali die Base frei gemacht. Die Base wird in Äther aufgenommen und der Äther abdestilliert. Der Rückstand wird dann in Alkohol gelöst und mit 85%iger Phosphorsäure neutralisiert, wobei das 1-Phenyl-1-(p-methoxyphenyl)-3-dimethylamino-propanphosphat auskristalliert. F. 158°.

Beispiel 4

23 g β-Dimethylaminopropiophenon werden in 50 ccm absolutem Äther gelöst und zu einer Grignardlösung aus 3,9 g Magnesiumspänen und 35 g Bromhydrochinondimethyläther in Äther getropft. Dann gibt man 100 ccm Benzol hinzu und kocht 1 Stunde unter Rückfluß. Man gießt auf Eis, trennt die ätherische Lösung ab und schüttelt letztere mit verdünnter Salzsäure durch. Aus der salzsauren Lösung erhält man die Base als bald kristallisierende Substanz. Nach dem Umkristallisieren aus Hexahydrobenzol erhält man das 1-Phenyl-1-(2', 5'-dimethoxyphenyl)-3-dimethylamino-propanol-(1) in Form farbloser Kristalle vom Schmelzpunkt 146°, die sich wie vorher beschrieben weiterverarbeiten lassen.

Beispiel 5

In gleicher Weise erhält man aus 70 g β-Piperidino-3, 4-dimethoxypropiophenon in 300 ccm Benzol mit einer Grignardlösung aus 6,7 g Magnesiumspänen und 43,5 g Brombenzol in Äther das 1-Phenyl-1-(3', 4'-dimethoxyphenyl)-3-piperidinopropanol-(1), welches in Form des Oxalats zu farblosen Kristallen vom Schmelzpunkt 190° führt und sich ebenso wie die Propanole der vorherigen Beispiele dehydratisieren und dann hydrieren läßt. Das erhaltene 1-Phenyl-1-(3, 4-dimethoxyphenyl)-3-piperidinopropan-hydrochlorid schmilzt bei 184°. Das als Ausgangsstoff verwendete β-Piperidino-3, 4-dimethoxypropiophenon (Schmelzpunkt 113°) wird aus β-Chlor-3, 4-dimethoxypropiophenon und Piperidin gewonnen.

Beispiel 6

Zu einer Grignardlösung von 9,6 g Magnesium und 66 g Brombenzol in 400 ccm Äther läßt man eine Lösung von 50 g 1-Phenyl-3-methylbenzylaminopropanon-(1) in 50 ccm Äther zulaufen und kocht das Ganze 3 Stunden unter Rückfluß. Das Umsetzungsprodukt wird alsdann auf Eis gegossen und ausgeäthert. Die Ätherlösung wird mit Wasser gewaschen und eingedampft. Der kristalline Rückstand wird aus Hexahydrobenzol umkristallisiert. Man erhält das 1, 1-Diphenyl-3-methylbenzylaminopropanol-(1) vom Schmelzpunkt 110°.

20 g der erhaltenen Base werden in 60 ccm Phosphorsäure (85%ige) gelöst und 1 Stunde auf 130° erhitzt. Nach dem Abkühlen wird das Umsetzungsprodukt mit Wasser verdünnt, mit konzentrierter Natronlauge alkalisch gemacht und ausgeäthert. Die Ätherlösung wird über Natriumsulfat getrocknet und eingeengt. Es verbleibt als Rückstand ein gelbgefärbtes Öl, das sofort in Methanol gelöst, mit Salzsäure neutralisiert und mit Palladium und Wasserstoff hydriert wird. Nach Aufnahme von 2 Mol Wasserstoff ist die Hydrierung beendet. Es wird alsdann vom Katalysator abgesaugt und die alkoholische Flüssigkeit im Vakuum eingeengt. Der kristalline Rückstand wird aus verdünntem Aceton umkristallisiert. Man erhält das 1, 1-Diphenyl-3-methylamino-propan-hydrochlorid vom Schmelzpunkt 178°.

Beispiel 7

Zu einer Grignardlösung von 4,8 g Magnesium und 31,5 g Brombenzol in 200 ccm Äther läßt man eine Lösung von 14,9 g 1-Phenyl-3-aminopropanon-(1) (Berichte der Deutschen Chemischen Gesellschaft, 41, 244) in 25 ccm Äther zulaufen und kocht einige Stunden unter Rückfluß. Das Produkt wird wie in den vorhergehenden Beispielen beschrieben aufgearbeitet. Nach Erhitzen der erhaltenen Propanolbase mit 85%iger Phosphorsäure und anschließender Hydrierung der hierbei entstandenen Anhydroverbindung erhält man das 1, 1-Diphenyl-3-amino-propan. Das Hydrochlorid der neuen Verbindung zeigt den Schmelzpunkt 217°.

Patentanspruch:

Verfahren zur Herstellung von γ, γ-Diarylpropyl-aminen, dadurch gekennzeichnet, daß man in β-Stellung basisch substituierte Propiophenone mit metallorganischen Arylverbindungen zur Umsetzung bringt, aus den entstandenen tertiären Carbinolen Wasser abspaltet und die erhaltenen ungesättigten Aminoverbindungen hydriert.

© 9605 3. 55

Translation of German Patent No. 925 468

METHOD FOR PREPARING γ,γ-DIARYLPROPYLAMINES

In Patents Nos. 766 207 and 908 136 the preparation of basic diarylalkyl compounds or diarylcycloalkyl compounds is described, which is done by linking diarylmethane, whose aryl groups may also be connected to one another, with basic alkyl groups or cycloalkyl groups, or by treating diarylacetic acid compounds containing a basic group with agents that split off the acid group.

In Patent No. 875 660 a method is also described which is characterized in that β-tert.-aminopropionic acid ester is reacted with phenylmagnesiumhalogenides to form γ-tert.-amino-α,α-diphenylpropanol, water is split off from it, and the products are hydrogenated.

Now, in continuation of this work direction, it was found that one may also arrive at the same or similar compounds by reacting propiophenones, that are basically substituted in the β position, with metalloorganic aryl or aralkyl compounds, converting the tertiary carbinols obtained by dehydration into the corresponding unsaturated bases, and by hydrogenating the latter. For example, one may react β-piperidinopropiophenone with phenylmagnesium bromide, and heat the carbinol obtained for a short time with hydrochloric acid on a water bath. From this, one obtains γ,γ-diphenylallylpiperidine, which is converted to γ,γ-diphenylpropylpiperidine by hydrogenation.

Compared to the methods named above, the present method has the advantage of being able to prepare more easily diarylpropylamines having different aryl groups among one another. The products coming about in the present method have therapeutic interest, and should, therefore, find application as such or for the preparation of other medicaments.

EXAMPLE 1

43 g β-piperidinopropiophenone, dissolved in 50 cc of ether are dripped into a phenylmagnesium bromide solution made up of 63 g bromobenzene and 9.6 g magnesium in 200 cc ether. The whole is then boiled for 4 hours under reflux. Then the liquid is poured onto a mixture of 500 parts by weight of ice and 100 parts by weight of concentrated hydrochloric acid. 1,1-diphenyl-3-piperidinopropanol-(1)-hydrochloride separates out as a crystalline precipitate. The compound is filtered off under suction, is washed with water and ethyl acetate, and is recrystallized from methanol with the addition of ether. The m.p. is 216 to 217°C. For the dehydration, 10 g of the base freed of the hydrochloride are dissolved in 30 cc of 85% phosphoric acid, and heated for 1 hour to 130°. After the cooling of the liquid, one dilutes using a three-fold to four-fold quantity of water, and makes alkaline with strong sodium hydroxide solution. The γ,γ-diphenylallylpiperidine separates out as an oil, and this is taken up in ether. The ether solution is neutralized using alcoholic hydrochloric acid, whereupon the γ,γ-diphenylallylpiperidine-hydrochloride separates out, which melts at 204 to 206° after recrystallization from acetone.

For the purpose of converting to the saturated compound, the hydrochloride obtained is dissolved in alcohol and is

hydrogenated with palladium and hydrogen. After absorption of the calculated quantity of hydrogen, one withdraws from the catalyst and evaporates off the liquid under vacuum. The residue is recrystallized from alcohol while adding ether. The 1,1-diphenyl-3-piperidinopropane-hydrochloride melts at 215 to 216°. The conversion takes place according to the following reaction scheme:

see original, page 2, lines 25 to 42 and 88 to 105.

EXAMPLE 2

35 g β-dimethylaminopropiophenone, dissolved in 50 cc ether, are dripped, while cooling, into a Grignard solution made up of 53 g p-bromotoluene and 7.2 g magnesium in 300 cc ether. After boiling for 3 hours under reflux, the whole contents are poured over ice, and the ether liquid is separated. The ether solution is washed with water, dried briefly over sodium sulfate, and evaporated to a low volume. Thereby 1-phenyl-1-p-tolyl-3-dimethylamino-propanol-(1) crystallizes from the ether solution, which is washed with ether and petroleum ether. The hydrochloride of the base melts at 185°.

10 g of the 1-phenyl-1-p-tolyl-3-dimethylamino-propanol-(1) are dissolved in 30 cc of 85% phosphoric acid and heated for 1 hour to 130 to 135°. After cooling, the liquid is diluted with water and made alkaline with strong sodium hydroxide solution. The base separating during this process is taken up in ether. The ethereal liquid is dried over sodium sulfate and the ether is distilled off. As the residue from the ether solution, γ-phenyl-γ-p-tolyl-allyl-dimethylamine remains in oily form. The oily base is dissolved in alcohol, is neutralized with alcoholic hydrochloric acid and hydrogenated using palladium and hydrogen.

After absorption of the calculated quantity of hydrogen, one filters off from the catalyst and evaporates off the alcoholic solution under vacuum. The residue obtained is dissolved in hot ethyl acetate and is filtered. After a brief period of cooling, 1-phenyl-1-o-tlyl-3-dimethylamino-propane-hydrochloride crystallizes out from the ethyl acetate solution. m.p. is 156^0.

EXAMPLE 3

50 g β-dimethylaminopropiophenone are dissolved in 100 cc absolute ether and dripped into a Grignard solution, prepared from 8.2 g magnesium turnings, 100 cc absolute ether and 64 g p-bromoanisol. Then the mixture is poured over ice , the ether solution is separated and is shaken thoroughly with dilute hydrochloric acid. The acid solution is made alkaline with sodium hydroxide solution, and the separated base is taken up in ether. The residue boils in a vacuum under 2 mm pressure at 200 to 210^0. By dissolving in a little hexahydrobenzene **[cyclohexane]**, after a short period the 1-phenyl-1-p-methoxyphenyl-3-dimethylamino-propanol-(1) crystallizes out in the form of colorless crystals having an m.p. of 118 to 119^0. 13.8 g of the base are dissolved in 280 cc of 10% hydrochloric acid and completely evaporated on a steam bath. The residue is taken up in water, made alkaline with calcium carbonate and extracted with ether. The ether solution is evaporated, neutralized with alcoholic hydrochloric acid and hydrogenated using palladium and hydrogen. After absorption of 1.2 l hydrogen, one filters off from the catalyst and the alcoholic solution is evaporated. The base is removed from the residue using alkali. The base is taken up in ether and the ether is distilled off. The residue is then dissolved in alcohol and neutralized with 85% phosphoric acid, whereupon the 1-phenyl-1-

(p-methoxyphenyl)-3-dimethylamino-propane-phosphate crystallizes out. Fusion point: 158°.

EXAMPLE 4

23 g β-dimethylaminopropiophenone are dissolved in 50 cc absolute ether, and dripped into a Grignard solution made of 3.9 g magnesium turnings and 35 g bromohydroquinonedimethylether in ether. Added to this are 100 cc benzene, and the mixture is boiled for 1 hour under reflux. It is poured over ice, the ether solution is separated and shaken thoroughly with dilute hydrochloric acid. From the hydrochloric acid solution, one obtains the base as a substance that will soon crystallize. After recrystallizing from cyclohexane, one obtains 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-dimethylamino-propanol-(1) in the form of colorless crystals having an m.p. of 146°, which may be processed further, as described above.

EXAMPLE 5

In the same manner one obtains 1-phenyl-1-(3',4'-dimethoxyphenyl)-3-piperidino-propanol-(1) from 70 g β-piperidino-3,4-dimethoxypropiophenone in 300 cc benzene with a Grignard solution of 6.7 g magnesium turnings and 43.5 g bromobenzene in ether, which, in the form of the oxalate, leads to colorless crystals having an m.p. of 190°, and which, just as the propanols of the previous examples, may be dehydrated and then hydrogenated. The 1-phenyl-1-(3',4'-dimethoxyphenyl)-3-piperidino-propane-hydrochloride melts at 184°. The β-piperidino-3,4-dimethoxypropiophenone (m.p. 113°) is obtained from β-chloro-3,4-dimethoxypropiophenone and piperidine.

EXAMPLE 6

A solution of 50 g 1-phenyl-3-methylbenzylaminopropanol-(1) in 50 cc ether is run into a Grignard solution of 9.6 g magnesium and 66 g bromobenzene in 400 cc ether, and the whole contents are boiled for 3 hours under reflux. The conversion product is then poured over ice and extracted with ether. The ether solution is washed with water and evaporated down. The crystalline residue is recrystallized from cyclohexane. 1,1-diphenyl-3-methylbenzylaminopropanol-(1) is obtained, having an m.p. of 110^0.

20 g of the base thus obtained are dissolved in 60 cc of 85% phosphoric acid and are heated for 1 hour to 130^0. After cooling, the conversion product is diluted with water, made alkaline with concentrated sodium hydroxide solution and is extracted with ether. The ether solution is dried over sodium sulfate and evaporated down. A yellow-colored oil remains as the residue, and it is immediately dissolved in methanol, neutralized with hydrochloric acid and hydrogenated using palladium and hydrogen. After absorption of 2 mol of hydrogen the hydrogenation is terminated. The contents are filtered off under suction from the catalyst, and the alcoholic liquid is evaporated down under vacuum. The crystalline residue is recrystallized from diluted acetone. 1,1-diphenyl-3-methylamino-propane-hydrochloride is obtained, having an m.p. of 178^0.

EXAMPLE 7

A solution of 14.9 g 1-phenyl-3-aminopropanone-(1) (Berichte der Deutschen Chemischen Gesellschaft, 41,244) in 25 cc ether is run into a Grignard solution of 4.8 g magnesium and 31.5 g bromobenzene in 200 cc ether, and the whole contents are boiled

for some hours under reflux. The product is prepared as in the preceding examples. After heating of the obtained propanol base with 85% phosphoric acid and subsequent hydrogenation of the anhydrous compound obtained thereby, one obtains 1,1-diphenyl-3-amino-propane. The hydrochloride of the new compound has an m.p. of 217^0.

What is claimed is:

1. A method for preparing γ,γ-diarylpropylamines, wherein propiophenones basically substituted in the β position are brought to conversion with metallo-organic aryl compounds, water is split off from the tertiary carbinols created, and the unsaturated amino compounds obtained are hydrogenated.

BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

Int. Cl.: C 07 c
C 07 d

Deutsche Kl.: 12 q - 1/02

AUSLEGESCHRIFT 1216318

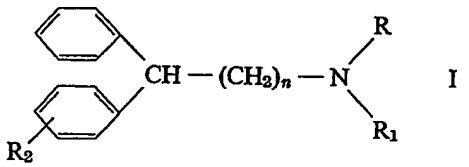
Nummer: 1 216 318
Aktenzeichen: K 48245 IV b/12 q
Anmeldetag: 15. November 1962
Auslegetag: 12. Mai 1966

Verfahren zur Herstellung von Diphenylalkylaminen

Anmelder:
Farbwerke Hoechst Aktiengesellschaft
vormals Meister Lucius & Brüning, Frankfurt/M.

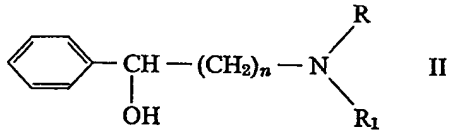
Als Erfinder benannt:
Dipl.-Chem. Dr. rer. nat. Josef Klosa, Berlin

Gegenstand der Erfindung ist ein Verfahren zur Herstellung von Diphenylalkylaminen der allgemeinen Formel I



I

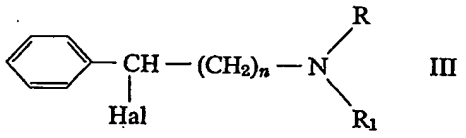
in der R Wasserstoff oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, R_1 Wasserstoff oder einen gegebenenfalls verzweigten Alkylrest mit 1 bis 4 Kohlenstoffatomen, der durch gegebenenfalls inert substituierte Alkyl- oder Arylreste substituiert sein kann, wobei R und R_1 auch gemeinsam mit dem Stickstoffatom Glieder eines heterocyclischen Ringes sein können, R_2 Wasserstoff, Halogen, Alkyl- oder Alkoxy-gruppen bedeuten, und *n* für die Zahl 1 oder 2 steht, das dadurch gekennzeichnet ist, daß man 1-Phenyl-1-hydroxy-alkylamine der allgemeinen Formel II



II

in der R, R_1 und *n* die oben angegebene Bedeutung besitzen, entweder

a) zunächst mit Halogenierungsmitteln behandelt und anschließend die erhaltenen Halogenverbindungen der allgemeinen Formel III



III

in der Hal ein Halogenatom bedeutet, mit einem aromatischen Kohlenwasserstoff der Formel R_2H in Gegenwart von Lewis-Säuren umsetzt oder

b) unmittelbar mit einem aromatischen Kohlenwasserstoff R_2H in Gegenwart einer Lewis-Säure umsetzt.

Es ist bereits bekannt, Diphenylmethan dadurch herzustellen, daß entweder Benzylchlorid oder Benzylalkohol in Gegenwart von Lewis-Säuren mit Benzol umgesetzt wird (vgl. »Bulletin de la société Chimiques de Paris«, Bd. 33 (1880), S. 337; »Journal of the American Chemical Society«, Bd. 59 (1937), S. 470 und 471, Bd. 61 (1939), S. 1522, linke Spalte, vorletzter Absatz, Bd. 62 (1940), S. 1623 und 1624, und »Berichte der deutschen Chemischen Gesellschaft«, Bd. 72, 1939, S. 1521, letzter Absatz, bis S. 1423, Abs. 1 und S. 1424, Abs. 4 a).

Gemäß dem erfindungsgemäßen Verfahren werden jedoch basisch substituierte Benzylverbindungen mit Aromaten in Gegenwart von Lewis-Säuren umgesetzt, d. h., es werden sekundäre Alkohole bzw. Chloride umgesetzt, während nach den erwähnten Literaturstellen primäre Alkohole bzw. Chloride als Ausgangsstoffe verwendet werden. Die Friedel-Crafts-Reaktion verläuft jedoch bereits bei primären Alkoholen und Chloriden keineswegs einheitlich, wie beispielsweise aus Fieser, »Lehrbuch der organischen Chemie«, 4. Auflage, 1916, S. 634 und 637, zu entnehmen ist. Daß die Friedel-Crafts-Reaktion mit sekundären Alkoholen noch weitaus unübersichtlicher verläuft, ergibt sich z. B. aus den Berichten der deutschen chemischen Gesellschaft, Bd. 72, S. 1415, Zeile 1 bis 7 von unten, unter 4.).

Bei der Anwesenheit einer Aminogruppe in β- oder α-Stellung hätte man bei der Friedel-Crafts-Reaktion die Bildung eines cyclischen Ammoniumsalzes (vgl. z. B. Angew., Bd. 72, 1960, S. 960) erwarten können, welches unter Polymerisation oder Umlagerung zu störenden Nebenreaktionen führen würde. Weiterhin war bei dem erfindungsgemäßen Verfahren die Hydraminspaltung der als Ausgangsstoffe verwendeten Arylalkanolamine zu erwarten

(vergleiche z. B. Archiv der Pharmazie, Bd. 289 [1956], S. 470).

Demgegenüber verläuft das erfindungsgemäße Verfahren jedoch überraschenderweise völlig einheitlich und führt daher mit ausgezeichneten Ausbeuten zu den gewünschten Verfahrensprodukten.

Einige der Verfahrensprodukte sind beispielsweise aus den deutschen Patentschriften 1 111 642 oder 1 100 031 bekannt.

Die bisherigen Synthesen dieser Verbindungen gehen im allgemeinen von Körperklassen aus, in welchen die Diphenylmethangruppe vorgebildet ist. So wird beispielsweise nach der deutschen Patentschrift 1 111 642 1,1-Diphenylpropylamin-(3) unter reduzierenden Bedingungen mit Phenylaceton kondensiert oder 1,1-Diphenylpropionaldehyd-(3) mit primären Aminen, z. B. Phenylisopropylamin, unter reduzierenden Bedingungen umgesetzt. Die Herstellung von 1,1-Diphenylpropylamin-(3) erfordert jedoch mehrere Reaktionsstufen (vergleiche z. B. J. Am. Chem. Soc., 33 [1905], S. 338, und 69 [1947], S. 358), wobei die Umsetzung mit Arylmagnesiumhalogeniden in wasserfreien Lösungsmitteln notwendig ist. Diese Umsetzungen haben wegen der erforderlichen absoluten Wasserfreiheit der Reagentien und wegen des Arbeitens in wasserfreiem Äther gewisse Nachteile.

Nach dem erfindungsgemäßen Verfahren werden diese Nachteile vermieden, da man nun die Verfahrensprodukte ausgehend von 1-Phenyl-1-hydroxy-alkylaminen herstellen kann, wobei erst nachträglich der zweite, gegebenenfalls inert substituierte Phenylrest mittels einer überraschenderweise glatt verlaufenden Friedel-Crafts-Reaktion eingeführt wird.

Nach dem erfindungsgemäßen Verfahren kann man 1-Phenyl-1-hydroxy-alkylamine mit Halogenierungsmitteln in 1-Phenyl-1-halogen-alkylamine der allgemeinen Formel III überführen, wobei mit besonderem Vorteil Thionylchlorid verwendet wird. Als 1-Phenyl-1-hydroxy-alkylamine können beispielsweise verwendet werden 1 - Phenyl - 1 - hydroxy - propylamin - (3), 1 - Phenyl - 1 - hydroxy - äthylamin - (2), 1 - Phenyl - 1 - hydroxypropyl - [N - isopropyl - (3)]-amin oder 1-Phenyl-1-hydroxy-2-(N)-morpholinoäthan. Bei der Umsetzung mit Thionylchlorid oder entsprechenden Chloriden werden die Halogenverbindungen der allgemeinen Formel III im allgemeinen als gut kristallisierende Hydrochloride erhalten.

Diese Verbindungen werden mit aromatischen Kohlenwasserstoffen der allgemeinen Formel R_2H der Friedel-Crafts-Reaktion unterworfen. Als aromatische Kohlenwasserstoffe können beispielsweise Benzol, Toluol oder Chlorbenzol verwendet werden. Als Friedel-Crafts-Katalysatoren verwendet man vorzugsweise Aluminiumchlorid, auch andere Metallhalogenide, wie Bortrifluorid oder Galliumchlorid, können verwendet werden.

Die Herstellung und die Isolierung der 1-Phenyl-1-halogenalkylamine der allgemeinen Formel II ist jedoch nicht unbedingt erforderlich. Man kann nach dem erfindungsgemäßen Verfahren die 1-Phenyl-1-hydroxy-alkylamine der allgemeinen Formel I auch unmittelbar mit einer Lewis-Säure, besonders wasserfreiem Aluminiumchlorid, mit einem aromatischen Kohlenwasserstoff der allgemeinen Formel R_2H umsetzen, wobei die Verfahrensprodukte in 80 bis 95%igen Ausbeuten erhalten werden.

Die Verfahrensprodukte stellen wertvolle Herz- und Kreislaufmittel dar, einige sind auch spasmolytisch und analgetisch wirksam. Die Verfahrensprodukte können auch als Zwischenprodukte zur Herstellung von Arzneimitteln verwendet werden.

Beispiel 1

15,1 g 1-Phenyl-1-hydroxy-propylamin werden mit 14,5 g Phenylaceton in 50 ml absolutem Benzol 30 Minuten gekocht, daraufhin wird das Benzol auf dem Wasserbad abdestilliert. Der ölige Rückstand wird mit 30 ml Methanol und 5 ml Wasser aufgenommen. In diese Lösung werden portionsweise 1,5 g Natriumborhydrid eingetragen. Dabei erwärmt sich das Reaktionsgemisch zum Schluß auf 40 bis 50°C. Man erhitzt nach Beendigung der Natriumborhydridzugabe noch 30 Minuten auf dem Wasserbad und destilliert Methanol und Wasser ab. Der ölige Rückstand wird mit Äther aufgenommen und mit alkoholischer Salzsäure bis zum Auftreten einer Trübung versetzt. Es kristallisiert das Hydrochlorid des 1-Phenyl-1-hydroxy-3-(N-phenylisopropylamino)-propan aus. Schmp.: 144 bis 146°C; Ausbeute: etwa 25 g.

Diese 25 g werden portionsweise in eine Lösung von 40 ml Thionylchlorid in 80 ml Benzol bei Zimmertemperatur eingetragen. Es setzt eine starke Salzsäureentwicklung und Schwefeldioxydentwicklung ein, nach kurzer Zeit scheidet sich das Hydrochlorid des Chlorierungsproduktes kristallin aus, welches abgesaugt und mit wenig Äther nachgewaschen wird. Ausbeute 30 g von 1-Phenyl-1-chlor-3-(N-phenylisopropylamin)-propan-hydrochlorid vom Schmp.: 138 bis 148°C. 10 g dieses Hydrochlorids werden in etwa 30 bis 40 ml Benzol suspendiert. Daraufhin werden 8 g wasserfreies, gepulvertes Aluminiumchlorid portionsweise eingetragen. Unter Salzsäureentwicklung färbt sich das Reaktionsgut tief dunkel, und die Temperatur steigt auf 40 bis 50°C. Man regelt die Zugabe des Aluminiumchlorids so, daß die Temperatur nicht über 50°C steigt und erwärmt schließlich noch 30 Minuten auf dem Wasserbad unter Rückfluß. Nach Erkalten wird das Reaktionsgut in ein Gemisch von 20 ml konzentrierter Salzsäure, 10 ml Wasser und 60 bis 100 g Eis gegossen. Nach einigen Stunden Stehen in der Kälte oder bei gewöhnlicher Temperatur scheidet sich das Hydrochlorid von 1,1-Diphenyl-3-(N-phenylisopropylamino)-propan in fast farblosen Kristallen aus. Rohausbeute: 14 g; Schmp.: 186 bis 188°C, aus Methanol Schmp.: 190 bis 192°C; Reinausbeute: 12,5 g.

Beispiel 2

In ein Gemisch von 16 ml Thionylchlorid und 30 ml Benzol werden 15 g 1-Phenyl-1-hydroxy-propylamin-(3) portionsweise eingetragen. Es tritt Erwärmung und starke Salzsäure- und Schwefeldioxydentwicklung ein. Nach Beendigung der Zugabe wird noch 10 bis 20 Minuten auf dem Wasserbad unter Rückfluß erwärmt, sodann läßt man einige Stunden stehen, wobei der Kolbeninhalt kristallin erstarrt. Durch Zugabe von Äther werden die Kristalle vollständig ausgeschieden, abgesaugt und getrocknet. Schmp.: 110 bis 112°C; Ausbeute: 10 g

1 - Phenyl - 1 - chlor - propylamin - (3) - hydrochlorid. 10 g des Hydrochlorids werden in 30 bis 40 ml absolutem Benzol suspendiert und 12 g wasserfreies und gepulvertes Aluminiumchlorid, wie im Beispiel 1, portionsweise zugeführt. Nachdem 30 Minuten auf dem Wasserbad erwärmt wurde, wird in einem Salzsäure-Wasser-Eis-Gemisch zersetzt. Es kristallisiert sofort das Hydrochlorid des 1,1-Diphenyl-propylamins-(3) aus. Schmp.: 204 bis 206°C; Ausbeute 13 g. Aus Alkohol umkristallisiert werden 12 g Reinausbeute erhalten.

Beispiel 3

10 g 1-Phenyl-1-hydroxy-2-(N-morpholino)-äthan werden in 25 bis 30 ml Benzol gelöst. In diese Lösung werden portionsweise 15 g wasserfreies Aluminiumchlorid eingetragen, wobei eine starke Erwärmung eintritt. Man regelt die Zuführung von Aluminiumchlorid in der Weise, daß das Benzol nicht zum Sieden kommt. Nach Beendigung der Zugabe von Aluminiumchlorid wird noch 30 Minuten auf dem Wasserbad zum Sieden erhitzt, abkühlen gelassen und dann das Reaktionsgemisch, welches aus zwei Schichten, einer schweren Ölschicht und einer leichteren Benzolschicht besteht, in ein Gemisch von Eiswasser und konzentrierter Salzsäure gegossen. Es tritt Trübung ein, und nach einigen Minuten erstarrt das Ganze zu einem perlglänzenden Kristallbrei. Die Kristalle werden abgesaugt, mit wenig eiskaltem Wasser gewaschen. Man erhält 15 g des Hydrochlorids von 1,1-Diphenyl-2-(N-morpholino)-äthan. Die Umkristallisation erfolgt durch Lösen in heißem Isopropylalkohol und Zusatz von Äther. Schmp.: 211 bis 213°C; Reinausbeute: 13 g.

Beispiel 4

5 g 1-Phenyl-1-hydroxy-2-(N-benzylamino)-äthan werden in 15 bis 20 ml Toluol gelöst. In diese Lösung werden 6 bis 8 g wasserfreies und gepulvertes Aluminiumchlorid eingetragen. Man regelt die Zufuhr des Aluminiumchlorids so, daß das Toluol nicht zum Sieden kommt. Schließlich wird noch 30 Minuten auf dem Wasserbad zum Sieden erhitzt, abkühlen gelassen und mit einem Gemisch von Eiswasser mit konzentrierter Salzsäure zersetzt. Nach einigen Stunden Stehen hat sich das Hydrochlorid des 1-Phenyl-1-(p-methylphenyl)-2-(N-benzylamino)-äthans fast vollständig abgeschieden. Roh-Schmp.: 192 bis 194°C. Aus Isopropanol und Äther erhält man farblose Nadeln vom Schmp.: 203 bis 205°C; Reinausbeute: 92%.

Beispiel 5

12 g Styroloxyd werden mit 13,5 g D-Phenylisopropylamin vermischt und mehrere Stunden auf 100 bis 120°C erhitzt. Man erhält 1-Phenyl-1-hydroxy - 2 - (N - phenylisopropylamino) - äthan als schwer bewegliches, fast farbloses Öl. In diese Benzollösung werden 20 g wasserfreies Aluminiumchlorid portionsweise dergestalt eingetragen, daß das Benzol nicht zum Sieden kommt. Es entsteht ein schwachgelbgefärbtes Reaktionsgemisch, in welchem das Aluminiumchlorid fast vollständig gelöst ist. Das Reaktionsgemisch wird noch 30 Minuten unter Rückfluß auf dem Wasserbad zum Sieden erhitzt, abkühlen gelassen und mit Eis-Wasser-Salzsäure 1 : 1 zersetzt. Es scheidet sich das Hydrochlorid des 1,1-Diphenyl-2-(N-phenyl-isopropylamino)-äthans als dickes, fast farbloses Öl ab. Dieses Öl wird dekantiert, erneut mit Wasser durchgerührt und schließlich unter Kühlung mit 20%iger Natronlauge behandelt, wobei sich die freie Base abscheidet, die mit Äther ausgeschüttelt wird. Die Ätherlösung wird mit wasserfreiem Natriumsulfat getrocknet und der Äther dann abdestilliert. Das zurückbleibende Öl wird mit einer alkoholischen Lösung von Maleinsäure behandelt, wobei das Maleinat kristallin ausfällt; dieses wird aus Alkohol und Äther umkristallisiert. Schmp.: 168 bis 170°C; Ausbeute: 88%, berechnet auf eingesetztes Styroloxyd.

Beispiel 6

14 g 1-Phenyl-1-hydroxy-2-amino-äthan werden mit 13,5 g Phenyl-aceton in 40 ml Methanol gelöst. Es werden 4 ml Wasser und portionsweise 1,5 g Natriumborhydrid zugefügt. Nachdem das Reaktionsgemisch 1 Stunde bei gewöhnlicher Temperatur gestanden hat, werden Methanol und Wasser im Vakuum vollständig abgedampft. Der Rückstand stellt ein Öl dar, welches in 40 ml Toluol aufgenommen wird und mit 20 g wasserfreiem Aluminiumchlorid, und wie im Beispiel 5 beschrieben, behandelt wird. Es resultiert 1-Phenyl-1-p-methylphenyl-2-(phenylisopropyl-amino)-äthan als farbloses, schwer bewegliches Öl, welches mit Maleinsäure in das Maleinat vom Schmp.: 166 bis 168°C übergeführt wird. Nach Umkristallisieren aus Methanol und Äther werden 35 g reines Maleinat erhalten.

Beispiel 7

11,5 ml β-Piperidino-propiophenon, dargestellt nach der Mannich-Reaktion aus Acetophenon, Paraformaldehyd und Piperidino-hydrochlorid, werden in 30 ml Methanol und 4 ml Wasser gelöst. Unter Rühren werden innerhalb von 15 bis 20 Minuten 1,1 g Natriumborhydrid portionsweise zugefügt. Gegen Ende der Zugabe tritt Erwärmung auf 40 bis 50°C ein. Man läßt das Reaktionsgemisch noch 2 bis 3 Stunden stehen und gießt es dann in die 3- bis 5fache Menge Wasser ein. Es scheidet sich ein dickes Öl ab, welches nach Reiben mit einem Glasstab kristallin erstarrt. Es wird abgesaugt und mit Wasser gewaschen. Aus Alkohol und Wasser umkristallisiert erhält man 9 g 1-Phenyl-1-hydroxy-3-N-piperidino-propan vom Schmp.: 54 bis 56°C.

7 g dieser freien Base werden portionsweise in eine Lösung von 6 ml Thionylchlorid in 10 ml Benzol eingetragen. Es tritt unter Erwärmung sofort Reaktion ein, alles geht in Lösung. Nach 4 Stunden Stehen wird mit Äther verdünnt. Man erhält 8 g 1 - Phenyl - 1 - chlor - 3 N - piperidino - propan - hydrochlorid als farblose Kristalle vom Schmp.: 156 bis 158°C.

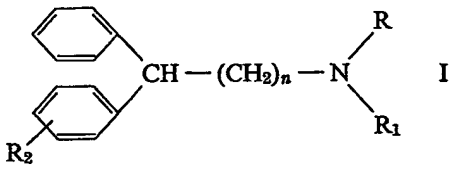
5 g dieser Verbindung oder 5 g 1-Phenyl-1-hydroxy-3-N-piperidinopropan werden in etwa 20 ml thiophenfreiem Benzol suspendiert, dazu werden 3 bis 5 g wasserfreies Aluminiumchlorid eingetragen. Der Verlauf der Reaktion ist wie im Beispiel 1. Man erhält in 85%iger Ausbeute das Hydrochlorid von 1,1 - Diphenyl - 3 - N - piperidino - propan vom Schmp.: 208 bis 210°C.

In analoger Weise werden in durchschnittlich 85%igen Ausbeuten erhalten:

1,1-Diphenyl-3-dimethylamino-propan-hydrochlorid, Schmp.: 166 bis 168°C.
1,1-Diphenyl-3-diäthylamino-propan-hydrochlorid, Schmp.: 142 bis 144°C.
1,1-Diphenyl-3-morpholino-propan-hydrochlorid, Schmp.: 202 bis 204°C.
1,1-Diphenyl-3-pyrrolidino-propan-phosphat, Schmp.: 159 bis 161°C.
1-Phenyl-1-(4'-methyl-phenyl)-3-dimethyl-amino-propan-hydrochlorid, Schmp.: 162 bis 164°C.

Patentanspruch:

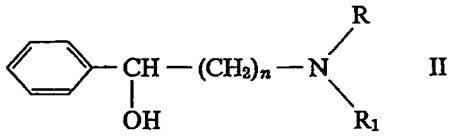
Verfahren zur Herstellung von Diphenylalkyl-aminen der allgemeinen Formel I



I

in der R Wasserstoff oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, R_1 Wasserstoff oder einen gegebenenfalls verzweigten Alkylrest mit 1 bis 4 Kohlenstoffatomen, der durch gegebenenfalls inert substituierte Alkyl- oder Arylreste substituiert sein kann, wobei R und R_1 auch gemeinsam mit dem Stickstoffatom Glieder eines heterocyclischen Ringes sein können, R_2 Wasserstoff, Halogen, Alkyl- oder Alkoxy-gruppen bedeuten und n für die Zahl 1 oder 2 steht, dadurch gekennzeichnet, daß man

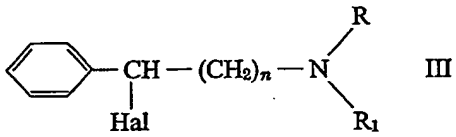
1-Phenyl-1-hydroxy-alkylamine der allgemeinen Formel II



II

in der R, R_1 und n die oben angegebene Bedeutung besitzen, entweder

a) zunächst mit Halogenierungsmitteln behandelt und anschließend die erhaltenen Halogenverbindungen der allgemeinen Formel III



III

in der Hal ein Halogenatom bedeutet, mit einem aromatischen Kohlenwasserstoff der Formel R_2H in Gegenwart von Lewis-Säuren umsetzt oder

b) unmittelbar mit einem aromatischen Kohlenwasserstoff R_2H in Gegenwart einer Lewis-Säure umsetzt.

In Betracht gezogene Druckschriften:
Deutsche Patentschriften Nr. 925 468, 1 100 031, 1 111 642;
deutsche Auslegeschrift Nr. 1 056 618:
Bull. Soc. chim. France, 33, S. 337 (1880);
J. Amer. chem. Soc., 59, S. 470 und 471 (1937); 61, S. 1522 (1939); 62, S. 1623 und 1624 (1940);
Ber. dtsch. chem. Ges. 72, S. 1421 bis 1423 (1939); 74, S. 1438 (1941);
Liebigs Ann. Chem., 603, S. 197 (1957).

609 568/551 5.66 ⊕ Bundesdruckerei Berlin

Translation of Patent Application Published for Opposition

1216318

METHOD FOR PREPARING DIPHENYLALKYLAMINES

The subject matter of the present invention is a method for preparing diphenylalkylamines of the general formula I,

see original I

in which R means hydrogen or an alkyl group having 1 to 3 carbon atoms, R_1 means hydrogen or possibly a branched alkyl group having 1 to 4 carbon atoms, which may be substituted by possibly inertly substituted alkyl groups or aryl groups, R and R_1 also being able to be members of a heterocyclic ring in common with the nitrogen atom, R_2 means hydrogen, a halogen, an alkyl group or an alkoxy group, and n stands for the number 1 or 2, which is characterized in that 1-phenyl-1-hydroxy-alkylamine of the general formula II

see original II

in which R, R_1 and n have the meaning given above, is either

a) first treated with halogenating means and subsequently the halogen compounds obtained, of the general formula

see original III

in which Hal means a halogen atom, are reacted with an aromatic hydrocarbon of the formula R_2H in the presence of Lewis acids, or

b) is reacted directly with an aromatic hydrocarbon R_2H in the presence of a Lewis acid.

It is known that one may prepare diphenylmethane by reacting either benzyl chloride or benzyl alcohol with benzene in the presence of Lewis acids (cf. "Bulletin de la société Chimique de Paris", vol. 33 (1880), p. 337; "Journal of the American Chemical Society", vol. 59 (1937), p. 470 and 471, vol. 61 (1939), p. 1522, left column, next to last paragraph, vol. 62 (1940), p. 1623 and 1624, and "Reports of the German Chemical Society", vol. 72, 1939, p. 1521, last paragraph to p. 1423, par. 1 and p. 1424, par. 4a).

According to the method according to the present invention, however, basically substituted benzyl compounds are reacted with aromatic compounds in the presence of Lewis acids, that is, secondary alcohols or chlorides are reacted, whereas, according to the places in the literature mentioned, primary alcohols or chlorides are used as the starting material. However, the Friedel-Crafts reaction does not run uniformly, even in the case of primary alcohols and chlorides, as may be seen in Fieser, "Textbook of Organic Chemistry", 4th edition, 1916, p. 634 and 637. The fact that the Friedel-Crafts reaction runs considerably less clearly for secondary alcohols may be inferred, for example, from Berichte der deutschen Chemischen Gesellschaft (Reports of the German Chemical Society), vol. 72, p. 1415, lines 1 through 7 from the bottom, under 4.).

In the presence of an amino group in the β or the α position, one might expect, in the Friedel-Crafts reaction, the formation of a cyclic ammonium salt (cf., for example, ref., vol. 72, 1960, p. 960), which by polymerization or molecular rearrangement would lead to disturbing side reactions. Furthermore, in the method according to the present invention, one might expect the hydramine decomposition of the arylalkanolamines used as the

starting materials (cf., for example, Archiv der Pharmazie (Archive of Pharmacy), vol. 289 [1956], p. 470).

By contrast, however, the method according to the present invention surprisingly runs completely uniformly **[homogeneously]**, and therefore leads to the desired method products at excellent yields.

Some of the method products are known, for example, from German patent documents 1 111 642 or 1 100 031.

Syntheses of these compounds, up to this point in time, have generally started from types of compounds in which the diphenylmethane group is preformed. Thus, for example, according to German Patent 1 111 642, 1,1-diphenylpropylamine-(3) is condensed with phenylacetone under reducing conditions, or 1,1-diphenylpropionaldehyde-(3) is reacted with primary amines, e.g. phenyisopropylamine under reducing conditions. The preparation of 1,1-diphenylpropylamine-(3), however, requires several reaction steps (cf., for instance, J. Am. Chem. Soc., 33 [1905], p.338, and 69 [1947], p. 358), where reaction with arylmagnesium halogenides in water-free solvents is required. These reactions have certain disadvantages, because of the required absolute absence of water of the reagents, and because of having to work with water-free ether.

According to the method according to the present invention, these disadvantages are avoided, since one is now able to prepare the method products starting from 1-phenyl-1-hydroxyalkylamines, in which only subsequently the second, possibly inertly substituted phenyl group is introduced, using a surprisingly smoothly running Friedel-Crafts reaction.

According to the method according to the present invention, using halogenizing agents, one is able to convert 1-phenyl-1-hydroxyalkylamine to 1-phenyl-1-halogen-alkylamine of the general formula III, for which thionyl chloride is used with especial advantage. As 1-phenyl-1-hydroxy-alkylamine-(3), one may use, for example, 1-phenyl-1-hydroxy-propylamine-(3), 1-phenyl-1-hydroxy-ethylamine-(2), 1-phenyl-1-hydroxypropyl-[N-isopropyl-(3)]-amine or 1-phenyl-1-hydroxy-2-(N)-morpholinoethane. In the conversion of thionyl chloride or corresponding chlorides, halogen compounds of the general formula III are generally obtained as well crystallized hydrochlorides.

These compounds are submitted to the Friedel-Crafts reaction with aromatic hydrocarbons of the general formula R_2H. As the aromatic hydrocarbons one may use, for example, benzene, toluene or chlorobenzene. As the Friedel-Crafts catalysts, preferably aluminum chloride is used, but also other metal halogenides, such as boron trifluoride or gallium chloride may be used.

However, the preparation and the isolation of the 1-phenyl-1-halogenalkylamines of the general formula II is not absolutely necessary. According to the method according to the present invention, the 1-phenyl-1-hydroxy-alkylamines of the general formula I may be converted directly, using a Lewis acid, especially anhydrous aluminum chloride, using an aromatic hydrocarbon of the general formula R_2H, in which the method products are obtained in a yield of 80 to 95%.

The method products represent valuable heart and circulation preparations, and some have spasmolytic and analgesic effects. The method products may also be used as intermediate products for preparing pharmaceuticals.

EXAMPLE 1

15.1 g 1-phenyl-1-hydroxy-propylamine are boiled with 14.5 g phenylacetone in 50 ml absolute benzene for 30 minutes, and then the benzene is distilled off on a water bath. The oily residue is taken up in 30 ml methanol and 5 ml water. To this solution is added 1.5 g sodium hydroborate, in portions. During the course of this, the reaction mixture heats up finally to 40 to 50°C. After the addition of the sodium hydroborate, the mixture is heated for 30 minutes more on the water bath, and then the methanol and water are distilled off. The oily residue is taken up in ether and laced with alcoholic hydrochloric acid until it turns cloudy. The hydrochloride of 1-phenyl-1-hydroxy-3-(N-phenylisopropylamino)-propane crystallizes out. m.p.: 144 to 146°C; yield: approximately 25 g.

These 25 g are introduced in portions to a solution of 40 ml of thionyl chloride in 80 ml of benzene. A strong hydrochloric acid development and sulfur dioxide development set in, and, after a short while, the hydrochloride of the chlorination product comes out of solution in crystalline form, is filtered off under suction and rewashed with a little ether. The yield is 30 g of 1-phenyl-1-chloro-3-(N-phenylisopropylamine)-propane hydrochloride, having an m.p. of 138 to 148°C. 10 g of this hydrochloride are suspended in ca. 30 to 40 ml benzene. Then, 8 g anhydrous powdered aluminum chloride are added in portions. During the formation of hydrochloric acid, the reaction product turns to a very dark shade, and the temperature rises to 40 to 50°C. One should regulate the addition of the aluminum chloride so that the temperature does not rise above 50°C, and the mixture is finally still heated for 30 minutes on the water bath, under reflux. After cooling, the reaction product is poured into a

mixture of 20 ml water and 60 to 100 g of ice. After a few hours of standing in the cold or at room temperature, the hydrochloride of 1,1-diphenyl-3-(N-phenylisopropylamino)-propane comes down in almost colorless crystals. Crude yield: 14 g; m.p.: 186 to 188°C, from methanol m.p. 190 to 192°C; pure yield: 12.5 g.

EXAMPLE 2

15 g 1-phenyl-1-hydroxy-propylamine-(3) are placed in portions into a mixture of 16 ml thionyl chloride and 30 ml benzene. The mixture heats up and strong development of hydrochloric acid and sulfur dioxide takes place. At the end of the addition, heating is continued for 10 to 20 minutes on a water bath under reflux, the mixture is allowed to stand for a few hours, whereupon the contents of the flask solidify to crystals. The crystals are completely separated by the addition of ether, are filtered and dried. m.p. 110 to 112°C; yield: 10 g 1-phenyl-1-chloro-propylamine-(3)-hydrochloride. 10 g of the hydrochloride are suspended in 30 to 40 ml of absolute benzene, and 12 g anhydrous and powdered aluminum chloride are added in portions, as in Example 1. After heating for 30 minutes on a water bath, the material is decomposed in a mixture of hydrochloric acid, water and ice. The hydrochloride of 1,1-diphenyl-propylamine-(3) immediately crystallizes out. m.p.: 204 to 206°C; yield: 13 g. A pure yield of 12 g is obtained by recrystallizing from alcohol.

EXAMPLE 3

10 g 1-phenyl-1-hydroxy-2-(N-morpholino)-ethane are dissolved in 25 to 30 ml of benzene. Into this solution, 15 g anhydrous aluminum chloride are placed in portions, whereupon intense heating takes place. The addition of aluminum chloride is

regulated in such a way that the benzene does not come to a boil. After the addition of aluminum chloride, the mixture is heated to a boil for 30 minutes on a water bath, is allowed to cool, and then the reaction mixture, which is made up of two layers, a heavy oil layer and a lighter benzene layer, is poured into a mixture of ice water and concentrated hydrochloric acid. Cloudiness appears, and after a few minutes the whole mixture solidifies to a pearly crystal paste. The crystals are filtered off under suction and washed with a little ice-cold water. The yield is 15 g of the hydrochloride of 1,1-diphenyl-2-(N-morpholino)-ethane. Recrystallization is performed by dissolving in hot isopropyl alcohol and the addition of ether. m.p.: 211 to 213^{0}C; pure yield: 13 g.

EXAMPLE 4

5 g 1-phenyl-1-hydroxy-2-(N-benzylamino)-ethane are dissolved in 15 to 20 ml toluene. Into this solution, 6 to 8 g anhydrous and powdered aluminum chloride are placed. The addition of aluminum chloride is regulated in such a way that the toluene does not come to a boil. Finally, heating is carried on to boiling for 30 minutes on a water bath, the mixture is cooled and decomposed using a mixture of ice water and concentrated hydrochloric acid. After a few hours of standing, the hydrochloride of the 1-phenyl-1-(p-methylphenyl)-2-(N-benzylamino-ethane has separated out almost completely. Crude m.p.: 192 to 194^{0}C. From isopropyl alcohol and ether, one obtains colorless needles of m.p.: 203 to 205^{0}C; pure yield: 92%.

EXAMPLE 5

12 g styrene oxide are mixed with 13.5 g D-phenylisopropylamine and heated for several hours to 100 to 120^{0}C. One obtains 1-

phenyl-1-hydroxy-2-(N-phenylisopropylamino)-ethane as a viscous, almost colorless oil. To this benzene solution, 20 g anhydrous aluminum chloride are added in portions in such a way that the benzene does not come to a boil. A weakly yellow colored reaction mixture is created, in which the aluminum chloride has been almost completely dissolved. The reaction mixture is heated to boiling for thirty minutes on a water bath under reflux, is cooled, and decomposed using 1:1 ice water and hydrochloric acid. The hydrochloride of 1,1-diphenyl-2-(N-phenyl-isopropylamino)-ethane separates as a thick, almost colorless oil. This oil is decanted, once again stirred with water, and finally treated under cooling with 20% sodium hydroxide solution, whereupon the free base separates out, which is extracted with ether. The ether solution is dried using anhydrous sodium sulfate, and the ether is then distilled off. The residual oil is treated with an alcoholic solution of maleic acid, whereupon the maleate **[maleinate]** falls out in crystals; this is recrystallized from alcohol and ether. m.p.: 168 to 170°C; yield: 88%, calculated in relationship to the styrene oxide used.

EXAMPLE 6

14 g 1-phenyl-1-hydroxy-2-amino-ethane and 13.5 g phenylacetone are dissolved in 40 ml methanol. 4 ml water and, in portions, 1.5 g sodium boron hydride are added. After the reaction mixture has stood for 1 hour at room temperature, the methanol and the water are completely evaporated under a vacuum. The residue is an oil that is taken up in 40 ml toluene and treated with 20 g anhydrous aluminum chloride, as described in Example 5. The result is 1-phenyl-1-p-methylphenyl-2-(phenylisopropyl-amino)-ethane, as a colorless, viscous oil, which is converted, using

maleic acid, to the maleate, having m.p.: 166 to 168°C. After recrystallization from methanol and ether, 35 g pure maleate are obtained.

EXAMPLE 7

11.5 ml β-piperidino-propiophenone, prepared according to the Mannich reaction from acetophenone, paraformaldehyde and piperidino hydrochloride, are dissolved in 30 ml methanol and 4 ml water. While stirring, within 15 to 20 minutes, 1.1 g sodium boron hydride are added in portions. Towards the end of the addition, the mixture heats up to 40 to 50°C. The reaction mixture is allowed to stand for 2 to 3 hours, and is then poured into a 3-fold to 5-fold quantity of water. A thick oil separates out, which, after being triturated, using a glass rod, solidifies to crystals. It is filtered and washed with water. When recrystallized from alcohol and water, one obtains 9 g 1-phenyl-1-hydroxy-3-N-piperidino-propane, having m.p.: 54 to 56°C.

7 g of this free base are added in portions to a solution of 6 ml thionyl chloride in 10 ml benzene. There is an immediate reaction with heat, and solution is complete. After 4 hours of standing, the solution is diluted with ether. 8 g of 1-phenyl-1-chloro-3N-piperidino-propane hydrochloride are obtained as colorless crystals, m.p.: 156 to 158°C.

5 g of this compound or 5 g 1-phenyl-1-hydroxy-3-N-piperidinopropane are suspended in about 20 ml thiophene-free benzene, and 3 to 5 g anhydrous aluminum chloride are added to this. The course of the reaction is the same as in Example 1. One obtains an 85% yield of the hydrochloride of 1,1-diphenyl-3-N-piperidino-propane, m.p.: 208 to 210°C.

In an analogous fashion, one may obtain the following, at yields averaging 85%:

1,1-diphenyl-3-dimethylamino-propane hydrochloride, m.p.:166 to 168°C

1,1-diphenyl-3-diethylamino-propane hydrochloride, m.p.:142 to 144°C

1,1-diphenyl-3-morpholino-propane hydrochloride, m.p.:202 to 204°C

1,1-diphenyl-3-pyrrolidino-propane phosphate, m.p.:159 to 161°C

1,1-phenyl-1-(4'-methyl-phenyl)-3-dimethylamino-propane-hydrochloride, m.p.:162 to 164°C

What is claimed is:

1. A method for preparing diphenylalkylamines of the general formula I

see original I

in which R means hydrogen or an alkyl group having 1 to 3 carbon atoms, R_1 means hydrogen or possibly a branched alkyl group having 1 to 4 carbon atoms, which may be substituted by possibly inertly substituted alkyl groups or aryl groups, R and R_1 also being able to be members of a heterocyclic ring in common with the nitrogen atom, R_2 means hydrogen, a halogen, an alkyl group or an alkoxy group, and n stands for the number 1 or 2, wherein 1-phenyl-1-hydroxy-alkylamine of the general formula II

see original II

in which R, R_1 and n have the meaning given above, is either

a) first treated with halogenating means and subsequently the halogen compounds obtained, of the general formula

see original III

in which Hal means a halogen atom, are reacted with an aromatic hydrocarbon of the formula R_2H in the presence of Lewis acids, or

b) is reacted directly with an aromatic hydrocarbon R_2H in the presence of a Lewis acid.

Patents referred to:

see original.

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

(11) Publication number: 0 325 571 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 07.08.91 Bulletin 91/32

(51) Int. Cl.[5]: C07C 215/54, C07C 217/62, A61K 31/135

(21) Application number: 89850017.8

(22) Date of filing: 20.01.89

(54) New amines, their use and preparation.

Consolidated with 89901611.7/0354234 (European application No./publication No.) by decision dated 13.08.90.

(30) Priority: 22.01.88 SE 8800207

(43) Date of publication of application: 26.07.89 Bulletin 89/30

(45) Publication of the grant of the patent: 07.08.91 Bulletin 91/32

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
DK-A- 111 894
GB-A- 1 169 944
GB-A- 1 169 945
SE-A- 215 499
US-A- 3 446 901
CHEMICAL ABSTRACTS, vol. 97, No. 15, 11 October 1982, page 20, no. 120105n, Columbus, Ohio, US; MARKARYAN E. et al.: "Study of the relationship between permeability of arylalkylamine derivatives across a semipermeable membrane and their antiadrenergic activity"

(73) Proprietor: Kabi Pharmacia AB
S-751 82 Uppsala (SE)

(72) Inventor: Jönsson, Nils Ake
Fotbollsvägen 6
S-151 59 Södertälje (SE)
Inventor: Sparf, Bengt Ake
Drottningvägen 14A
D-142 00 Trangsund (SE)
Inventor: Mikiver, Lembit
Badstigen 6
S-153 00 Järna (SE)
Inventor: Moses, Pinchas
Dalvägen 6
S-132 00 Saltsjö-Boo (SE)
Inventor: Nilvebrant, Lisbet
Fältmarskalksvägen 9
S-161 35 Bromma (SE)
Inventor: Glas, Gunilla
Imatragatan 338
S-163 26 Spanga (SE)

(74) Representative: Kummelsten, Per-Arne et al
UPPSALA PATENTBYRA P.O. Box 9013
S-750 09 Uppsala (SE)

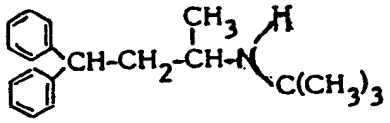
EP 0 325 571 B1

Description

The present invention relates to novel 3,3-diphenylpropylamino derivatives, to pharmaceutical compositions containing the same, and to the use of said derivatives for preparing drugs.

Swedish patent No. 215499 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

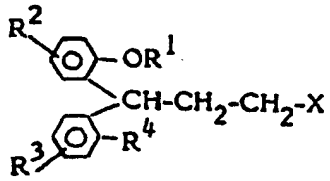


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect 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 have sympatholytic activity and carry aromatic substituents on the nitrogen atom.

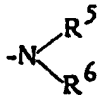
It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute toxicity.

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.

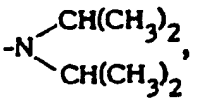
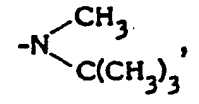
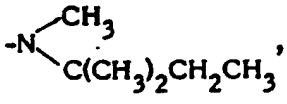
The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

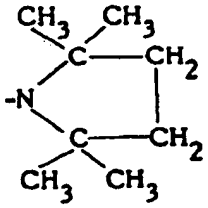
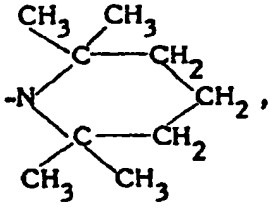
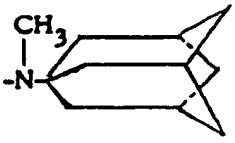
When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixt-

ure 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 following groups a)-f), each of which may carry one or more hydroxy groups.

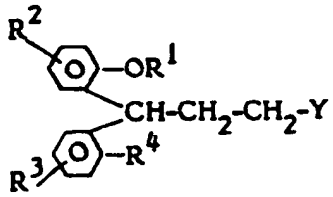
a)  , b)  , c)  ,

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 of 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

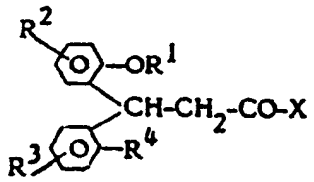
 III

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 group, preferably halogen or an alkyl or arylsulphonyloxy group, with an amine of formula IV

H – X IV

wherein X is as defined above, or

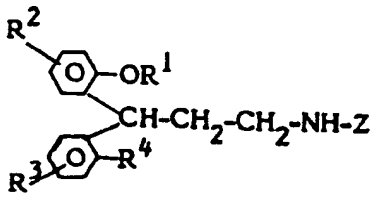
b) reducing a 3,3-diphenylpropionamide of formula V



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,

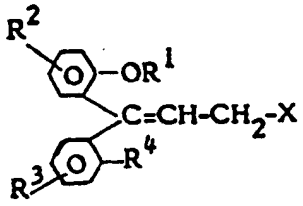
c) N-methylating a secondary 3,3-diphenylpropylamine VI



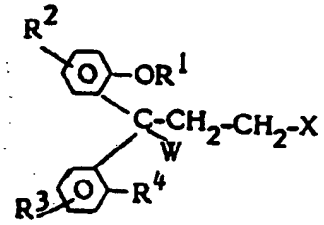
VI

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

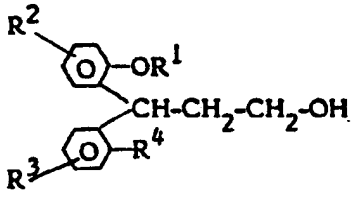
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

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.

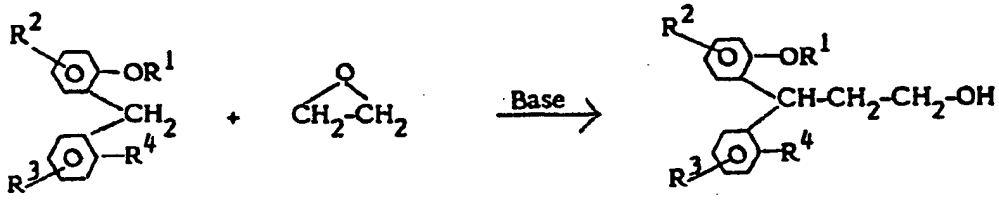
The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

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 :



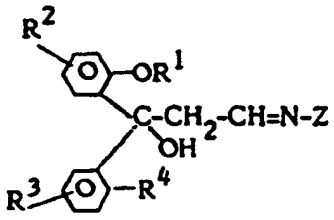
IX X VIII

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

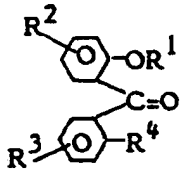
wherein R^1-R^4 and Z are as defined above, either in one step by catalytic hydrogenation, or by reduction to the corresponding saturated hydroxyamine, preferably using a complex metal hydride such as lithium aluminium hydride, followed by removal of the hydroxy group by catalytic reduction. As an alternative, 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 addition of a Schiff base of formula XII

$$CH_3 - CH{=}N - Z \quad XII$$

wherein Z is as defined above,

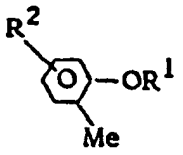
to a benzophenone of formula XIII



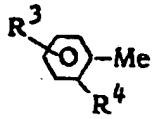
XIII

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

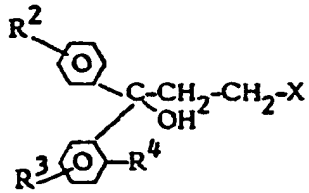


XIVa



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 accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions 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 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 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 invention will be further illustrated by the following non-limiting examples.

General

^{1}H-NMR spectra were run in $CDCl_3$ using a JEOL PMX60 spectrometer. 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-methylphenyl)-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

The above lactone (90 g, 0.32 mol) 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-methoxyphenyl)-3-phenylpropionate

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-Dibenzyloxyphenyl)-3-phenylpropanol (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-phenylpropanol (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 mol) 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 usual 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 obtained in 62% yield from the tosylate (XXXIV) of Example 4h).

NMR : δ 6.8-7.2 (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 : δ 6.5-7.3 (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-tetramethylpiperidine (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%) of crude title compound. By GC, it is at least 93% pure.

n) N-[3-(2-Benzyloxyphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine

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-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2-amino-2-methyl-propanol. 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° (acetone-ether).

$C_{23}H_{31}NO_6$ (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-dibenzyloxyphenyl)-3-phenylpropylamine (LVI), hydrochloride

The free base was obtained in 85% yield from the tosylate (XXXIII) of Example 4g). The HCl salt had m.p. 188° (ethanol-ether).

$C_{33}H_{38}NO_2Cl$ (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-methoxy-5-methylphenyl)-3-phenylpropylamine (LXVI), hydrochloride

The free base was obtained in the same way in 89% yield from the amine (LIII) of 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	Cl	9.08
Found		73.0		8.96		3.94		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	Cl	9.38
Found		69.9		8.56		3.53		8.92

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (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)propylamine (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-phenylpropylamine (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-phenylpropylamine (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)propylamine (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-phenylpropylamine (LXXVII)

This was obtained as an oil in 98% yield from the amine (LI) of Example 6b).
NMR : δ 6.9-7.3 (m 18H), 2.1 (s 3H), 1.0 (s 9H).

n) N-Methyl-N-tert.butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LXXVIII)

This was obtained as an oil in 97% yield 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-phenylpropylamine

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 evaporated, giving 32 g (94%) of N-[3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenylpropylidene]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-phenylpropylamine (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

Removal of O-protective groups

a) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (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-tetramethylpiperidine (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-phenylpropylamine (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
Found		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-hydroxyphenyl)propylamine (XCII), hydrochloride
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) requires:	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), hydrochloride
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. Recrystallization 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-Hydroxyphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine
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.

$C_{24}H_{33}NO_2 \cdot HCl \cdot 1/2\ H_2O$ (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.

$C_{20}H_{27}NO_2 \cdot HCl$ (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.

$C_{26}H_{33}NO \cdot HCl$ (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-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine

3-(2-Methoxy-5-methylphenyl)-3-phenylpropionic acid (12.8 g, 0.05 mol) (J.D. Simpson & H. Stephen, 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 solution. The mixture is chilled at about 4°C over-night whereupon the crystalline precipitate is filtered off, 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).

$C_{25}H_{28}O_3S$ (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°.

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 contracted hydrochloric acid. M.p. 130°.

$C_{22}H_{30}ClO_2N \cdot HCl \cdot H_2O$ (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 $\frac{1}{2}$ 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%.

$C_{22}H_{31}NO_2 \cdot HCl$ (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).

$C_{21}H_{28}NO_2 \cdot HCl$ (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-methylphenyl)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-hydroxyphenyl)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, 3×10^{-6}M, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol (3×10^{-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 3×10^{-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°C
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 3×10^{-7} M

The chosen doses give about 70% of maximal response. The agonist is added to the bath at 10-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 10 minutes noradrenaline is added. The next concentration of the test substance is added when the original response of the 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°C
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 : 5×10^{-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 dissolved in double distilled water. The solutions were prepared on the day of the experiment.

Procedure

White male mice, 25 g, were placed in a mouse holder. The tested compounds were given as i.v. bolus doses in one of the four tail-veins, with a volume of 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	Anticholi. 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
Terodilline (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 1 (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	$1.5x10^{-8}$	$5.5x10^{-6}$	$6x10^{-6}$	10^{-5}	30-40	40	
4a. (+)-isomer of 4 tartrate	$1.3x10^{-8}$		$6.5x10^{-6}$		10-20	20	
4b. (-)-isomer of 4 tartrate	$1.3x10^{-6}$		$6x10^{-6}$		10-20	20	
5	$4.9x10^{-9}$	$3.8x10^{-5}$	$3x10^{-5}$	10^{-5}	30-45	45	1-3
6	$2.0x10^{-7}$	$3x10^{-5}$	$6.5x10^{-5}$	$1.3x10^{-5}$	>20	>20	
7	$1.9x10^{-8}$	$5x10^{-5}$	$6.5x10^{-5}$	$3x10^{-6}$	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-Hl 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	

Example A

Preparation of 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

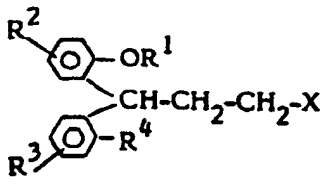
Preparation of capsules

	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.

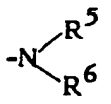
Claims

1. 3,3-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



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.

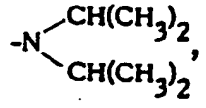
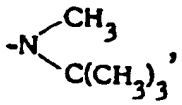
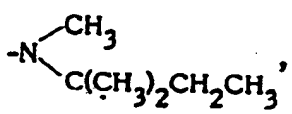
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^5 and R^6 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably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

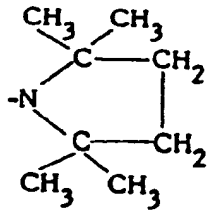
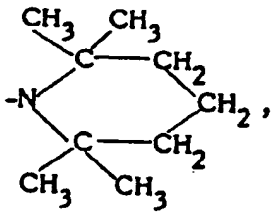
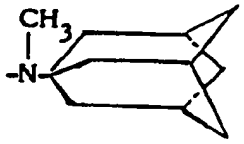
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein R^5 and R^6 taken together form a ring with the amine nitrogen.

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 of the following groups a)-f), each of 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 :

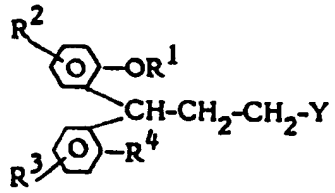
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,
N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine,
N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,
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-diphenylpropanol of formula III

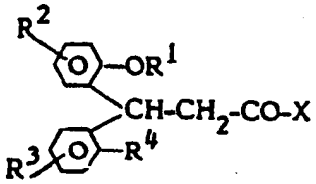


III

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

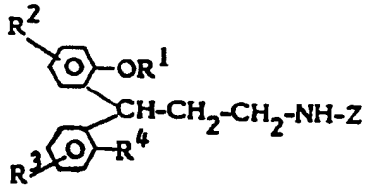
$$H-X \quad IV$$

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



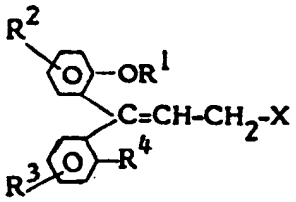
V

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

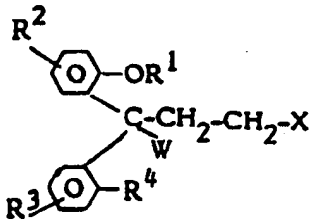


VI

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

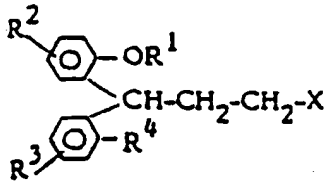
i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or

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.

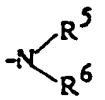
Patentansprüche

1. 3,3-Diphenylpropylamine der Formel I



I

worin R^1 für Wasserstoff oder Methyl steht, R^2, R^3 und R^4 unabhängig voneinander für Wasserstoff, Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfanoyl oder Halogen stehen, und X eine tertiäre Aminogruppe der Formel II



darstellt, worin R^5 und R^6 für nicht-aromatische Hydrocarbylgruppen stehen, die gleich oder verschieden sein können und die miteinander mindestens drei Kohlenstoffatome enthalten, und wobei R^5 und R^6 zusammen mit dem Aminstickstoff einen Ring bilden können, ihre Salze mit physiologisch annehmbaren Säuren, und wenn die Verbindungen in Form von optischen Isomeren vorliegen können, das racemische Gemisch und die individuellen Enantiomeren.

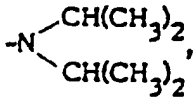
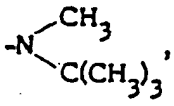
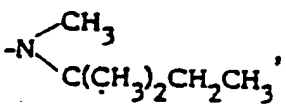
2. 3,3-Diphenylpropylamine nach Anspruch 1, **dadurch gekennzeichnet,** daß jedes R^5 und R^6 unabhängig für eine gesättigte Hydrocarbylgruppe, insbesondere gesättigte, aliphatische Hydrocarbylgruppen, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl oder Adamantyl, stehen, daß R^5 und R^6 miteinander mindestens drei, vorzugsweise mindestens vier Kohlenstoffatome, haben.

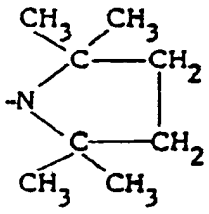
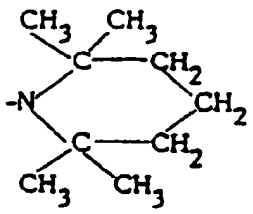
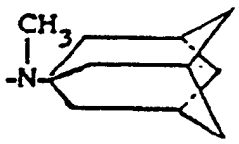
3. 3,3-Diphenylpropylamine nach Anspruch 1 oder 2, **dadurch gekennzeichnet,** daß R^5 und R^6 zusammengenommen mit dem Aminstickstoff einen Ring bilden.

4. 3,3-Diphenylpropylamine nach Anspruch 1, 2 oder 3, **dadurch gekennzeichnet,** daß R^5 und/oder R^6 mindestens einen Hydroxysubstituenten trägt.

5. 3,3-Diphenylpropylamine nach einem der vorstehenden Ansprüche, **dadurch gekennzeichnet,** daß mindestens eine von R^5 und R^6 eine verzweigte Kohlenstoffkette umfaßt.

6. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet,** daß X für eine der folgenden Gruppen a) bis f) steht, wobei jede davon mindestens einen Hydroxysubstituenten tragen kann:

a)  b)  c) 

d)  e)  f) 

7. 3,3-Diphenylpropylamine nach Anspruch 1, **dadurch gekennzeichnet,** daß sie aus der Gruppe, bestehend aus den folgenden Verbindungen, ihren Salzen mit physiologisch annehmbaren Säuren und wenn möglich, ihren Racematen und individuellen Enantiomeren ausgewählt sind :
N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamin,
N-Methyl-N-tert.-butyl-3-(2-hydroxyphenyl)-3-phenylpropylamin,
N-Methyl-N-tert.-butyl-3-(2,4-dihydroxypehynl)-3-phenylpropylamin,
N-Methyl-N-tert.-butyl-3,3-bis-(2-hydroxyphenyl)-propylamin,
N,N-Diisopropyl-3,3-bis-(2-hydroxyphenyl)-propylamin,
N,N-Diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamin,
N-Methyl-N-tert.-butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamin,
N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamin,
N-[3-(2-Methoxyphenyl)-3-phenylpropyl]-2,2,6,6-tetramethylpiperidin,
(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamin.

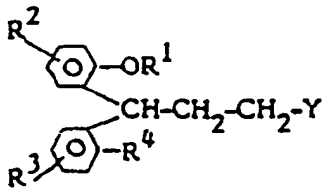
8. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 7 zur Verwendung als pharmazeutische Wirkstoffe, insbesondere als anticholinerge Mittel.

9. Pharmazeutisches Präparat, **dadurch gekennzeichnet,** daß es ein 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 7 und einen verträglichen pharmazeutischen Träger enthält.

10. Verwendung eines 3,3-Diphenylpropylamins nach einem der Ansprüche 1 bis 7 zur Herstellung eines anticholinergen Arzneimittels.

11. Verfahren zur Herstellung von 3,3-Diphenylpropylaminen nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet,** daß man

a) ein reaktiv verestertes 3,3-Diphenylpropanol der Formel III

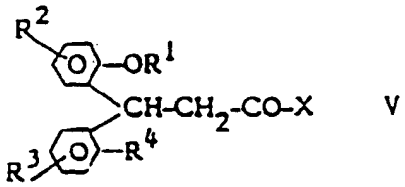
 III

worin R^1 bis R^4 wie oben definiert sind, wobei irgendwelche Hydroxygruppen geschützt sein können, und Y eine Austrittsgruppe ist mit einem Amin der Formel IV

H – X IV

worin X wie oben definiert ist, umsetzt oder

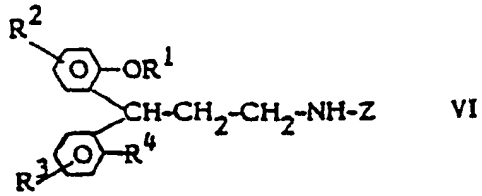
b) ein 3,3-Diphenylpropionamid der Formel V



V

worin R^1 bis R^4 und X wie oben definiert sind, und irgendwelche Hydroxygruppen geschützt sein können, reduziert oder

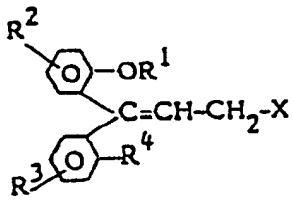
c) ein sekundäres 3,3-Diphenylpropylamin VI



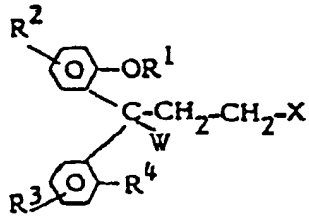
VI

worin R^1 bis R^4 wie oben definiert sind, und irgendwelche Hydroxygruppen geschützt sein können, und wobei Z die gleiche Bedeutung wie R^5 und R^6, ausgenommen Methyl, hat, N-methyliert oder

d) ein 3,3-Diphenylpropylamin der Formel VIIa oder VIIb



VIIa



VIIb

worin R^1 bis R^4 und X wie oben definiert sind, und irgendwelche Hydroxygruppen geschützt sein können, und W für eine Hydroxygruppe oder ein Halogenatom steht, reduziert, und

i) erforderlichenfalls Hydroxyschutzgruppen in den erhaltenen Verbindungen gewünschtenfalls nach Mono- oder Dihalogenierung eines oder beide der Phenylringe abspaltet, und/oder

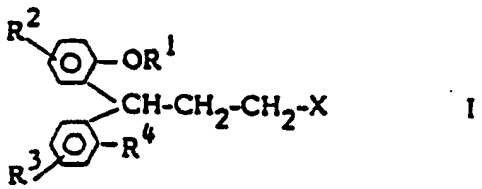
ii) gewünschtenfalls erhaltene Basen der Formel I in die Salze davon mit physiologisch annehmbaren Säuren umwandelt oder umgekehrt, und/oder

iii) gewünschtenfalls ein erhaltenes Gemisch von optischen Isomeren in die individuellen Enantiomeren auftrennt, und/oder

iv) gewünschtenfalls eine ortho-Hydroxygruppe in einer erhaltenen Verbindung der Formel I, worin R^1 Wasserstoff ist und/oder R^4 Hydroxy ist, methyliert.

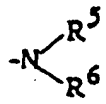
Revendications

1. 3,3-diphéylpropylamines de formule I



I

dans laquelle R^1 représente l'hydrogène ou un groupe méthyle, R^2, R^3 et R^4 représentent indépendamment l'hydrogène, un groupe méthyle, méthoxy, hydroxy, carbamoyle, sulfamoyle ou un halogène, et X représente un groupe amino tertiaire de formule II



dans laquelle R^5 et R^6 représentent des groupes hydrocarbonés non aromatiques qui peuvent être identiques ou différents et qui contiennent ensemble au mois trois atomes de carbone, et dans laquelle R^5 et R^6 peuvent former un cycle avec l'azote du groupe amine, leurs sels avec des acides acceptables du point de vue physiologique et, lorsque les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères individuels.

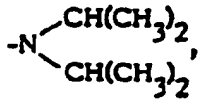
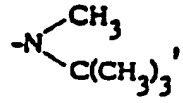
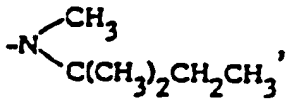
2. 3,3-diphénylpropylamines selon la revendication 1, dans lesquelles chacun des substituants parmi R^5 et R^6 représente indépendamment un groupe hydrocarboné saturé, en particulier des groupes hydrocarbonés aliphatiques saturés tels que alkyle en C_{1-8}, en particulier alkyle en C_{1-8}, ou adamantyle, R^5 et R^6 comprenant ensemble au moins trois, de préférence au moins quatre atomes de carbone.

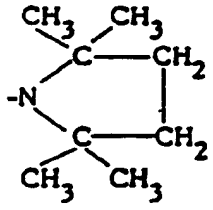
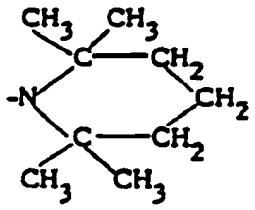
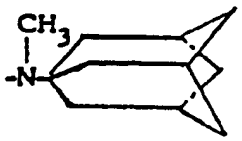
3. 3,3-diphénylpropylamines selon la revendication 1 ou 2, dans lesquelles R^5 et R^6 pris ensemble forment un cycle avec l'azote du groupe amine.

4. 3,3-diphénylpropylamines selon la revendication 1, 2 ou 3, dans lesquelles R^5 et/ou R^6 porte au moins un substituant hydroxy.

5. 3,3-diphénylprolylamines selon l'une quelconque des revendications précédentes, dans lesquelles au moins l'un des substituants R^5 et R^6 comprend une chaîne carbonée ramifiée.

6. 3,3-diphénylpropylamines selon l'une quelconque des revendications 1 à 5, dans lesquelles X représente l'un quelconque des groupes suivants a)-f), chacun de ces groupes pouvant porter au moins un substituant hydroxy :

a)  , b)  , c) 

d)  , e)  , f) 

7. 3,3-diphénylpropylamines selon la revendication 1, choisies dans le groupe formé par les composés suivants, leurs sels avec des acides acceptables du point de vue physiologique et, lorsque cela est possible, leurs racémates et leurs éniantiomères individuels :
N,N-diisopropyl-3-(2-hydroxy-5-méthylphényl)-3-phénylpropylamine,
N-méthyl-N-tert.butyl-3-(2-hydroxyphényl)-3-phénylpropylamine,
N-méthyl-N-tert.butyl-3-(2,4-dihydroxyphényl)-3-phénylpropylamine,
N-méthyl-N-tert.butyl-3,3-bis-(2-hydroxyphényl)propylamine,
N,N-diisopropyl-3,3-bis-(2-hydroxyphényl)propylamine,
N,N-diisopropyl-3-(2,5-dihydroxyphényl)-3-phénylpropylamine,
N-méthyl-N-tert.butyl-3-(2,5-dihydroxyphényl)-3-phénylpropylamine,
N,N-diisopropyl-3-(2-méthoxyphényl)-3-phénylpropylamine,
N-(3-(2-méthoxyphényl)-3-phénylpropyl)-2,2,6,6-tétraméthylpipéridine,
(+)-N,N-diisopropyl-3-(2-hydroxy-5-méthylphényl)-3-phénylpropylamine.

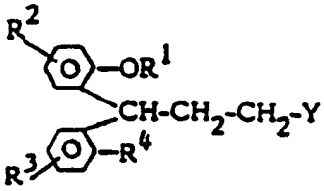
8. 3,3-diphénylpropylamines selon l'une quelconque des revendications 1 à 7 utilisables comme substances actives du point de vue pharmaceutique, en particulier comme agents anticholinergiques.

9. Composition pharmaceutique comprenant une 3,3-diphénylpropylamine selon l'une quelconque des revendications 1 à 7 et un véhicule compatible du point de vue pharmaceutique.

10. Utilisation d'une 3,3-diphénylpropylamine selon l'une quelconque des revendications 1 à 7 pour préparer un médicament anticholinergique.

11. Procédé de préparation des 3, 3-diphénylpropylamines selon l'une quelconque des revendications 1 à 7, comprenant :

a) la réaction d'un 3,3-diphénylpropanol estérifié de manière réactive de formule III



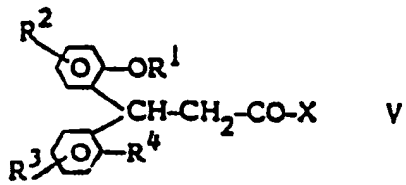
III

dans laquelle R^1-R^4 sont tels que définis ci-dessus, un groupe hydroxy quelconque peut être protégé et Y est un groupe partant, avec une amine de formule IV

$$H-X \quad IV$$

dans laquelle X est tel que défini ci-dessus, ou

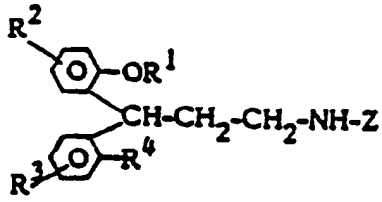
b) la réduction d'un 3,3-diphénylpropionamide de formule V



V

dans laquelle R^1-R^4 et X sont tels que définis ci-dessus et un groupe hydroxy quelconque peut être protégé, ou

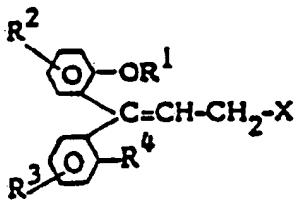
c) la N-méthylation d'une 3,3-diphénylpropylamine secondaire VI



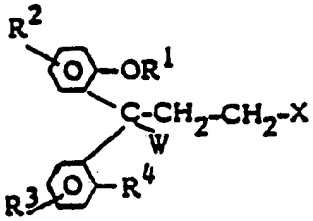
VI

dans laquelle R^1-R^4 sont tels que définis ci-dessus et un groupe hydroxy quelconque peut être protégé, et dans laquelle Z a la même signification que R^5 et R^6 à l'exception du méthyle, ou

d) la réduction d'une 3,3-diphénylpropylamine de formule VIIa ou VIIb



VIIa



VIIb

dans laquelle R^1-R^4 et X sont tels que définis ci-dessus et un groupe hydroxy quelconque peut être protégé et W représente un groupe hydroxy ou un atome d'halogène, et

i) si nécessaire le clivage des groupes protecteurs des groupes hydroxy dans les composés obtenus, si on le souhaite après mono ou dihalogénation de l'un des cycles phényle ou des deux, et/ou

ii) si on le souhaite la conversion des nases de formule I obtenues en leurs sels avec des acides acceptables du point de vue physiologique, ou vice versa, et/ou

iii) si on le souhaite la séparation d'un mélange d'isomères optiques obtenu en les énantiomères individuels, et/ou

iv) si on le souhaite la méthylation d'un groupe hydroxy en ortho dans un composé de formule I obtenu, dans lequel R^1 est un atome d'hydrogène et/ou R^4 est un groupe hydroxy.

(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)

(72) Inventors:
- **JOHANSSON, Rolf, Arne**
  S-141 38 Huddinge (SE)
- **MOSES, Pinchas**
  S-132 00 Saltsjö-Boo (SE)
- **NILVERBANT, Lisbeth**
  S-161 35 Bromma (SE)
- **SPARF, Bengt, Ake**
  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

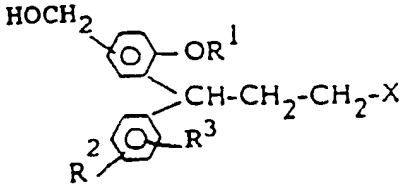
Printed by Jouve, 75001 PARIS (FR)

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.

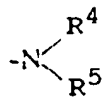
WO 89/06644 discloses 3,3-diphenylpropylamines having anticholinergic activity. In accordance with the present invention novel therapeutically active compounds have now been found, some of which are formed as metabolites in mammals when treated with the 3,3-diphenylpropylamines disclosed in the above-mentioned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

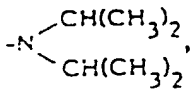
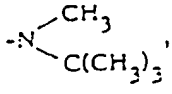
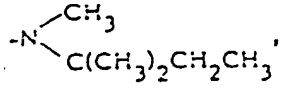
R^2 is preferably in 3-, 4- or 5-position.

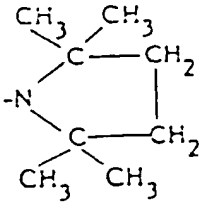
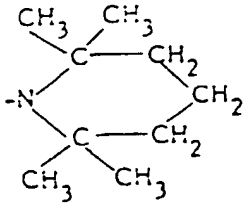
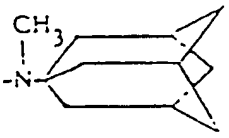
R^3 is preferably in 2-position with respect to the propylamine group.

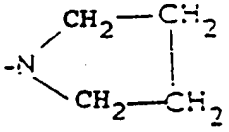
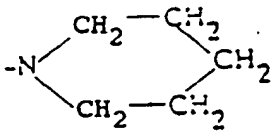
The $HOCH_2$-group is preferably in 5-position.

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) 

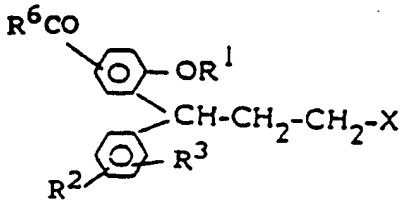
g)  , h) 

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

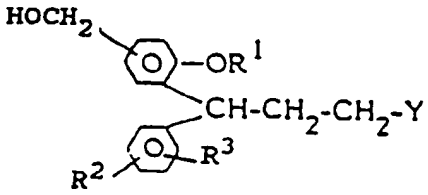
a) reducing the group R^6CO in a 3,3-diphenylpropylamine of formula III



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



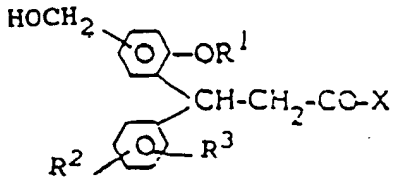
IV

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

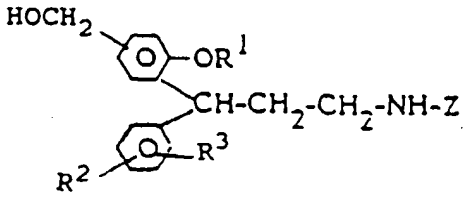
c) reducing a 3,3-diphenylpropionamide of formula VI



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

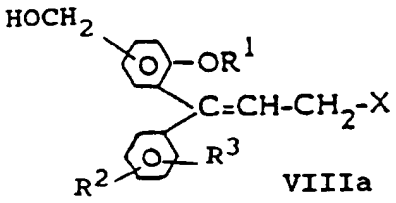
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



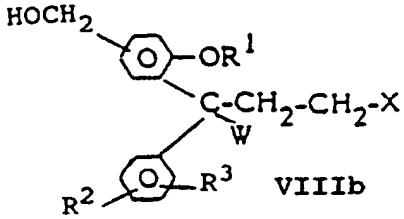
VII

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



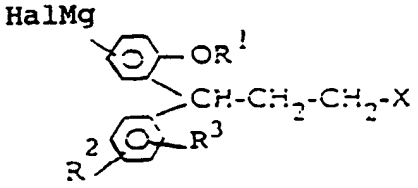
VIIIa



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,

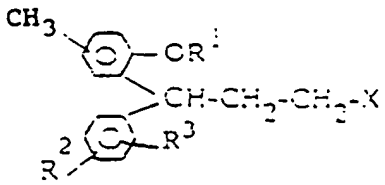
f) reacting a 3,3-diphenylpropylamine of formula IX



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 theoretical amount of hydrogen was consumed. The progress of the reaction was

monitored by gas chromatography. The mixture was then filtered through a pad of Celatom, and the solvent was removed by evaporation at a bath temperature <50°C. The resulting oil was dissolved in diethyl ether, and the ethereal solution was washed with water, dried over sodium sulfate and evaporated giving 22.2 g of a colourless oil. $[\alpha]^{22} = 16.7°$ (c = 4.9, ethanol).

To the above oil, dissolved in 2-propanol (50 g) was added S-(+)-mandelic acid (9.6 g, 0.06 mole) in 2-propanol (50 g). Dry diethyl ether (50 g) was added, and the solution was left for several hours. The resulting heavy, white crystals were filtered off and washed with a mixture of 2-propanol and diethyl ether (1:1 v/v) and then dried, yielding 25 g of the title compound which melted at 148°C. $[\alpha]^{22} = 38.3°$ (c = 5.1, methanol).

The 1-H N.M.R. spectrum was in accordance with the above structure.

Chiral purity as assessed by H.P.L.C. was >99%.

Elementary Anal.	Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
	Found	C: 72.9	H: 8.1	N: 3.0	O: 16.5

j2) (-)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium (-) mandelate

The title compound was obtained from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine in an analogous manner to that described in j1) above.

Elementary Anal.	Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
	Found	C: 73.2	H: 8.1	N: 3.0	O: 16.5

The free base had an optical rotation of $[\alpha]^{22} = -15.5°$ (c = 5.0, ethanol).

The 1-(-)-mandelic acid salt had a m.p. of 147-148°C and an optical rotation $[\alpha]^{22} = -37.9°$ (c = 4.7, methanol).

The optical purity as assessed by H.P.L.C. was >99 %.

Pharmacology

Pharmacological tests performed with one compound of the invention and three prior art compounds disclosed in the above mentioned WO 89/06644 will now be described. The following compounds were used:

(A) (+)N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, hydrochloride (WO 89/06644);
(B) N,N-diisopropyl-3-bis-(2-hydroxyphenyl)propylamine hydrochloride (WO 89/06644);
(C) (+)N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenylpropylamine, hydrochloride (WO 89/06644);
(D) N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine (-) mandelic acid salt (Example 1 above).

Raised index numerals in the text below refer to literature references listed at the end of the description.

Muscarinic Receptor Binding Studies

The tissue preparations and the general methods used have been described in detail elsewhere for the parotid gland[1], urinary bladder[2], heart[3] and cerebral cortex[3], respectively. Male guinea pigs (250-400 g body weight) were killed by a blow on the neck and exsanguinated. The brain was placed on ice for dissection of the cerebral cortex (grey matter only). Urinary bladders, hearts and parotid glands were dissected in a Krebs-Henseleit buffer (pH 7.4) containing 1 mM phenyl methyl sulfonyl fluoride (PMSF, a protease inhibitor). Dissected tissues were homogenized in an ice-cold sodium-potassium phosphate buffer (50 mM, pH 7.4) containing 1 mM PMSF, using a Polytron PT-10 instrument (bladder, heart, parotid) and a Potter-Elvehjem Teflon homogenizer (cortex). All homogenates were finally diluted with the ice-cold phosphate/PMSF buffer to a final protein concentration of ≤ 0.3 mg/ml and immediately used in the receptor binding assays. Protein was determined by the method of Lowry et al. (1951)[4], using bovine serum albumin as the standard.

The muscarinic receptor affinities of the unlabelled compounds A to D identified above were derived from competition experiments in which the ability to inhibit the receptor specific binding of (-)^{3}H-QNB (1-quinuclidinyl[phenyl-4-3H] benzilate, 32.9 Ci/mmole) was monitored as previously described[3,5]. Each sample contained 10 µl of (-)^{3}H-QNB (final concentration 2 nM), 10 µl solution of test compound and 1.0 ml tissue homogenate. Triplicate samples were incubated under conditions of equilibrium, i.e., at 25°C for 60 minutes (urinary bladder), 80 minutes (heart and cerebral cortex)

or 210 minutes (parotid gland), respectively. Non-specific binding was determined in the presence of 10 µM unlabelled atropine. Incubations were terminated by centrifugation[2], and the radioactivity in the pellets was determined by liquid scintillation spectrometry[2].

IC_{50}-values (concentration of unlabelled compound producing 50% inhibition of the receptor specific (-)^{3}H-QNB binding) were graphically determined from the experimental concentration-inhibition curves. Affinities, expressed as the dissociation constants K_i, were calculated by correcting the IC_{50} for the radioligand-induced parallel shift and differences in receptor concentration, using the method of Jacobs et al. (1975)[6]. The binding parameters for (-)^{3}H-QNB (K_D and receptor densities) used in these calculations were determined in separate series of experiments[1-3]. The K_i values obtained for bladder, heart, parotid and cortex, respectively, are presented in Table 1 below.

Functional in vitro studies

Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilize for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilization period.

Carbachol (carbamylcholine chloride) was used as the standard agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by three consecutive additions of a submaximal concentration (3×10^{-6} M) of carbachol. A complete concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}-values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1)[7], where [A] is the concentration of test compound.

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

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.

References

1. Nilvebrant, L.; Sparf, B. Muscarinic receptor binding in the parotid gland. Different affinities of some anticholinergic drugs between the parotid gland and ileum. Scand. J. Gastroenterol. 1982, 17 (suppl. 72), 69-77.

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.

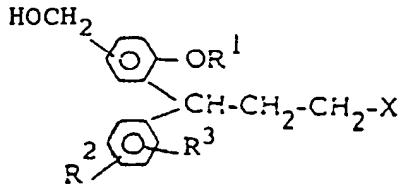
5. Nilvebrant, L.; Sparf, B. Differences between binding affinities of some antimuscarinic drugs in the parotid gland and those in the urinary bladder and ileum. Acta Pharmacol. et Toxicol. 1983 b, 53, 304-313.

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.

7. Schild, H. I. pAx and competitive drug antagonism. Br. J. Pharmacol. Chemother. 1949, 4, 277-280.

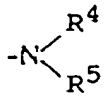
Claims

1. 3,3-Diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2 and R^3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



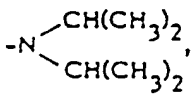
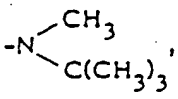
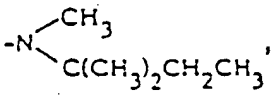
II

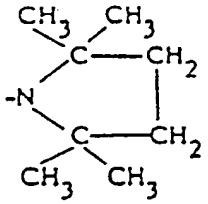
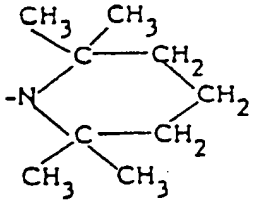
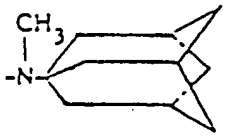
wherein each of R^4 and R^5 independently signify non-aromatic hydrocarbyl groups, which may carry one or more hydroxy groups and which together contain at least three carbon atoms, and wherein R^4 and R^5 may be joined to form a ring having no other heteroatom than the amine nitrogen, their salts with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

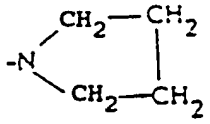
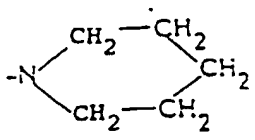
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^4 and R^5 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably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

3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^4 and R^5 comprises a branched carbon chain.

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

a)  , b)  , c)  ,

d)  , e)  , f) 

g)  , h) 

5. 3,3-Diphenylpropylamines according to any one of claims 1 to 4, wherein the $HOCH_2$-group is in 5-position, R^2 is hydrogen and R^3 is hydrogen or hydroxy, preferably in 2-position.

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

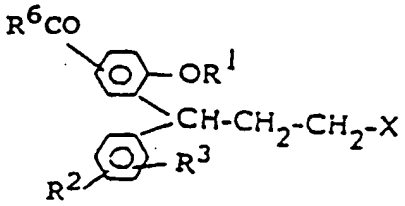
7. 3,3-Diphenylpropylamines according to any one of claims 1 to 6 for use as pharmaceutically active substances, especially as anticholinergic agents.

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

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

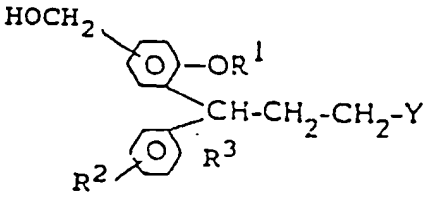
10. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1 to 6, comprising:

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



III

wherein R^1 to R^3 and X are as defined above, R^6 is hydrogen or R^7O, where R^7 is hydrogen, alkyl, alkenyl, alkynyl or aryl, and any hydroxy groups may be protected, such as by methylation or benzylation, or
b) reacting a reactively esterified 3,3-diphenylpropanol of formula IV

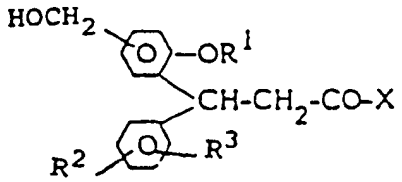


IV

wherein R^1 to R^3 are as defined above, any hydroxy groups may be protected, and wherein Y is a leaving group, with an amine of formula V

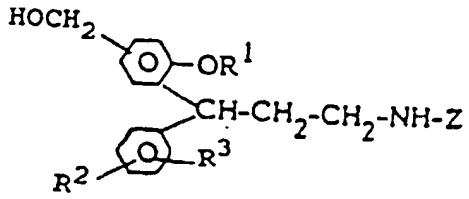
$$H\text{-}X \qquad V$$

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



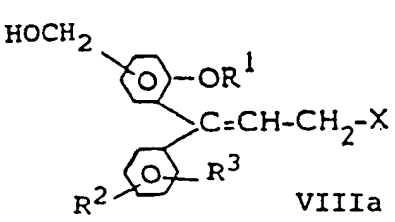
VI

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

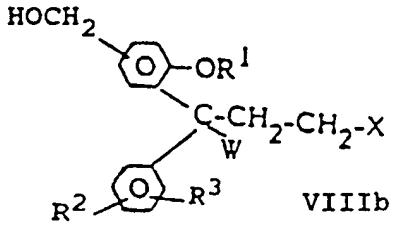


VII

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^4 and R^5 with the exception of methyl, or
e) reducing a 3,3-diphenylpropenamine of formula VIIIa or a 3,3-diphenylpropylamine of formula VIIIb

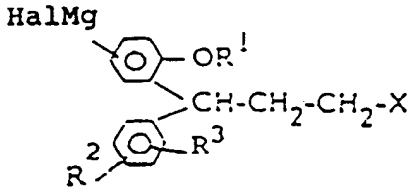


VIIIa



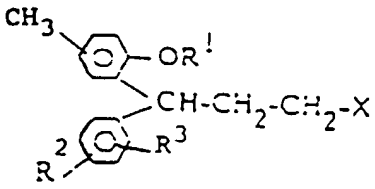
VIIIb

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, or
f) reacting a diphenylpropylamine of formula IX



IX

wherein R^1 to R^3 and X are as defined above, and Hal is halogen, with formaldehyde or a formaldehyde equivalent, or
g) oxidizing the methyl group of a diphenylpropylamine of formula X



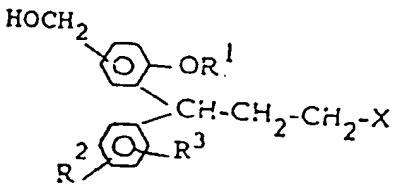
X

wherein R^1 to R^3 and X are as defined above, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono- or di-halogenation of one or both of the phenyl rings, and/or
ii) if desired converting the obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^3 is hydroxy.

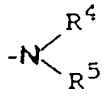
Patentansprüche

1. 3,3-Diphenylpropylamine der Formel I



I

worin R^1 für Wasserstoff oder Methyl steht, R^2 und R^3 unabhängig voneinander für Wasserstoff, Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen stehen und X für eine tertiäre Aminogruppe der Formel II



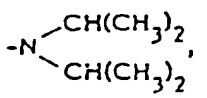
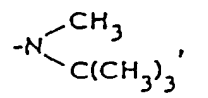
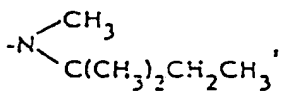
II

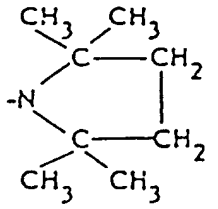
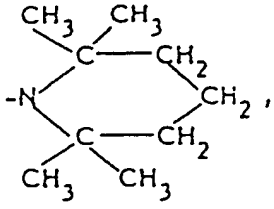
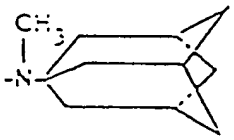
steht, in der jedes R^4 und R^5 unabhängig voneinander für nichtaromatische Kohlenwasserstoffgruppen steht, die eine oder mehrere Hydroxygruppen tragen können und die zusammen wenigstens drei Kohlenstoffatome enthalten und in der R^4 und R^5 miteinander verbunden sein können, um einen Ring zu bilden, der kein anderes Heteroatom besitzt als den Aminstickstoff, ihre Salze mit physiologisch annehmbaren Säuren und, wenn die Verbindungen in Form optischer Isomerer vorliegen können, die racemischen Gemische und die individuellen Enantiomere.

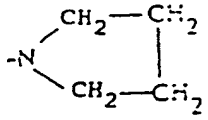
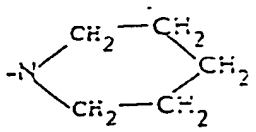
2. 3,3-Diphenylpropylamine nach Anspruch 1, dadurch **gekennzeichnet**, daß jedes R^4 und R^5 unabhängig voneinander eine gesättigte Kohlenwasserstoffgruppe, insbesondere eine gesättigte aliphatische Kohlenwasserstoffgruppe, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl bedeutet und R^4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

3. 3,3-Diphenylpropylamine nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß wenigstens ein Rest aus der Gruppe R^4 und R^5 eine verzweigte Kohlenstoffkette umfaßt.

4. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 3, dadurch **gekennzeichnet**, daß X für eine der folgenden Gruppen a) bis h) steht:

a)  , b)  , c)  ,

d)  , e)  , f) 

g)  , h) 

5. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 4, dadurch **gekennzeichnet**, daß die $HOCH_2$-Gruppe in der 5-Position ist, R^2 Wasserstoff und R^3 Wasserstoff oder Hydroxy, vorzugsweise in der 2-Position, ist.

6. 3,3-Diphenylpropylamine nach Anspruch 1, ausgewählt aus N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin, seinen Salzen mit physiologisch annehmbaren Säuren, Racemate und individuellen Enantiomere davon.

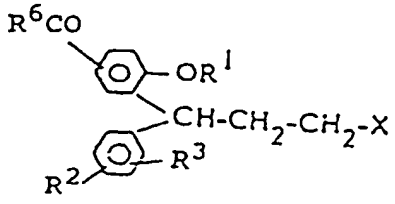
7. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 6 zur Verwendung als pharmazeutisch aktive Substanzen, insbesondere als anticholinerge Mittel.

8. Pharmazeutisches Mittel, umfassend ein 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 6 und vorzugsweise einen kompatiblen pharmazeutischen Träger.

9. Verwendung eines 3,3-Diphenylpropylamins nach einem der Ansprüche 1 bis 6 zur Herstellung eines anticholinergen Medikaments.

10. Verfahren zur Herstellung von 3,3-Diphenylpropylaminen nach einem der Ansprüche 1 bis 6, umfassend die folgenden Stufen:

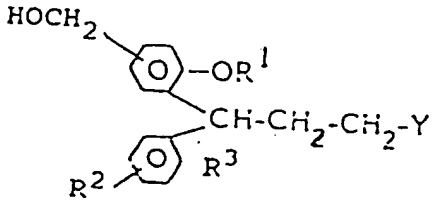
a) Reduktion der R^6CO-Gruppe eines 3,3-Diphenylpropylamins der Formel III



III

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, R^1 Wasserstoff oder R^7O ist, wobei R^1 Wasserstoff, Alkyl, Alkenyl, Alkinyl oder Aryl ist, und jegliche Hydroxygruppen z.B. durch Methylierung oder

Benzylierung geschützt sein können oder
b) Umsetzung eines reaktiv veresterten 3,3-Diphenylpropanols der Formel IV

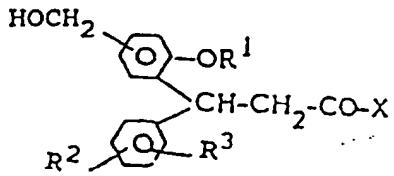


IV

in der R^1 bis R^3 die oben definierten Bedeutungen haben, jegliche Hydroxygruppen geschützt sein können und in der Y eine Austrittsgruppe ist, mit einem Amin der Formel V

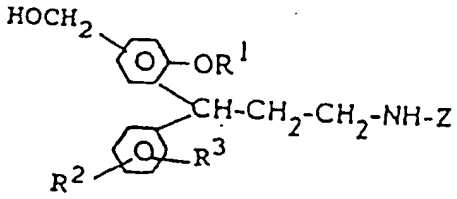
$$H-X \qquad V,$$

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



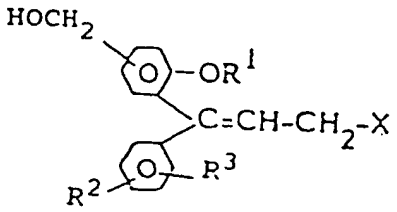
VI

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können, oder
d) N-Methylierung eines sekundären 3,3-Diphenylpropylamins der Formel VII

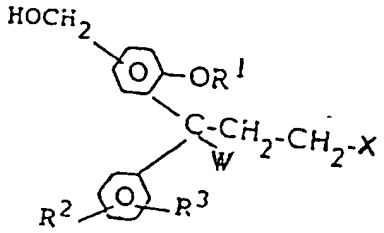


VII

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, und jegliche Hydroxygruppen geschützt sein können und in der Z die gleiche Bedeutung wie R^4 und R^5 mit Ausnahme von Methyl hat oder
e) Umsetzung eines 3,3-Diphenylpropenamins der Formel VIIIa oder eines 3,3-Diphenylpropylamins der Formel VIIIb



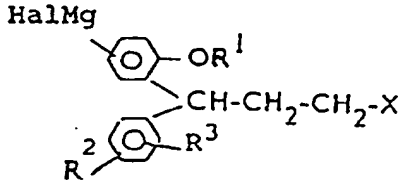
VIIIa



VIIIb

worin R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können und W für eine Hydroxygruppe oder ein Halogenatom steht oder

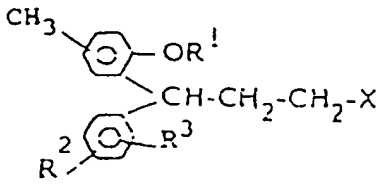
f) Umsetzung eines Diphenylpropylamins der Formel IX



IX

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und Hal für Halogen steht, mit Formaldehyd oder einem Formaldehyd-Äquivalent oder

g) Oxidation der Methylgruppe eines Diphenylpropylamins der Formel X



X

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und

i) falls nötig, Abspaltung der Hydroxyschutzgruppen in den erhaltenen Verbindungen, falls erwünscht nach Mono- oder Dihalogenierung eines oder beider Phenylringe und/oder

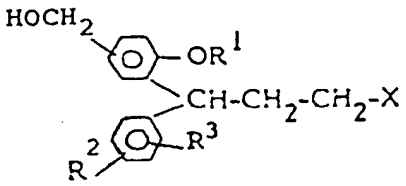
ii) falls gewünscht, Umwandlung der erhaltenen Basen der Formel I in die Salze davon mit physiologisch annehmbaren Säuren oder umgekehrt, und/oder

iii) falls gewünscht, Trennung eines erhaltenen Gemisches optischer Isomere in die individuellen Enantiomeren, und/oder

iv) falls gewünscht, Methylierung einer ortho-Hydroxygruppe in einer erhaltenen Verbindung der Formel I, in der R^1 für Wasserstoff und/oder R^3 für Hydroxy steht.

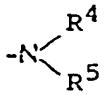
Revendications

1. 3,3-diphénylpropylamines de formule I



I

dans laquelle R^1 représente l'hydrogène ou un groupe méthyle, R^2 et R^3 représentent indépendamment l'hydrogène, un groupe méthyle, méthoxy, hydroxy, carbamoyle, sulfamoyle ou halogéno, et X représente un groupe amino tertiaire de formule II



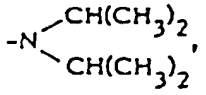
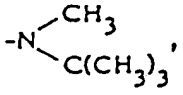
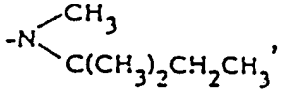
II

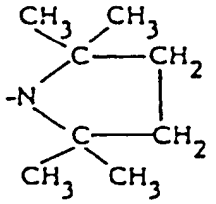
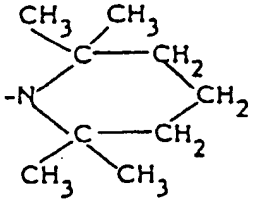
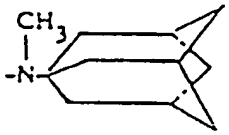
dans laquelle chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle non aromatique, qui peut porter un ou plusieurs groupes hydroxy, les groupes R^4 et R^5, conjointement, contenant au moins trois atomes de carbone, et dans laquelle R^4 et R^5 peuvent être joints en formant un noyau n'ayant aucun autre hétéroatome que l'atome d'azote d'amine, leurs sels formés avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères distincts.

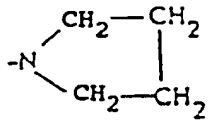
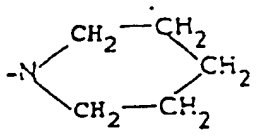
2. 3,3-diphénylpropylamines suivant la revendication 1, dans lesquelles chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle saturé, notamment un groupe hydrocarbyle aliphatique saturé tel qu'un groupe alkyle en C_1 à C_8, notamment alkyle en C_1 à C_6 ou un groupe adamantyle, les groupes R^4 et R^5, conjointement, comprenant au moins trois, de préférence au moins quatre atomes de carbone.

3. 3,3-diphénylpropylamines suivant la revendication 1 ou 2, dans lesquelles au moins un des groupes R^4 et R^5 comprend une chaîne carbonée ramifiée.

4. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 3, dans lesquelles X représente l'un quelconque des groupes a) à h) suivants :

a)  , b)  , c)  ,

d)  , e)  , f) 

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.

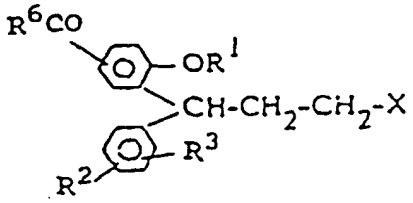
7. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, destinées à être utilisées comme substances pharmaceutiquement actives, notamment comme agents anticholinergiques.

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.

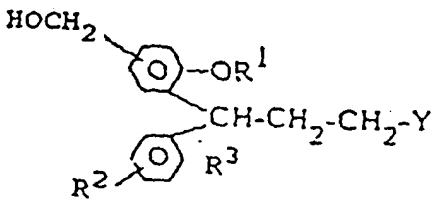
10. Procédé pour la préparation de 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, comprenant :

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

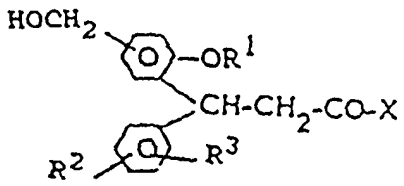


IV

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

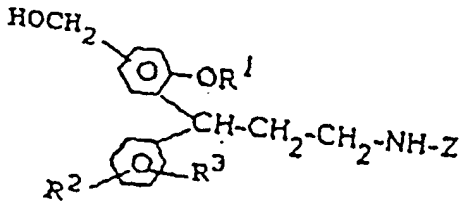
H - X V

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



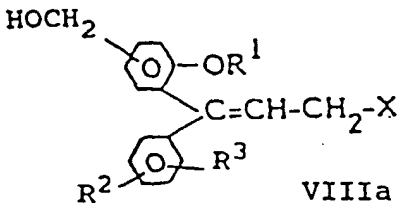
VI

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

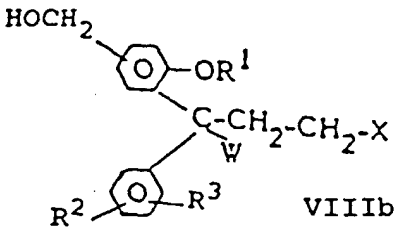


VII

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

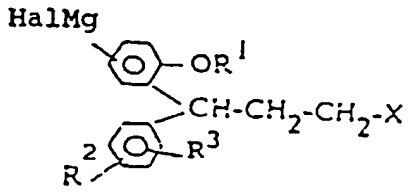


VIIIa



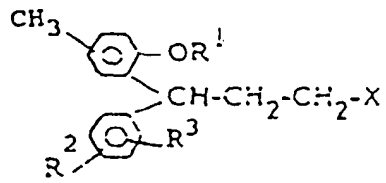
VIIIb

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.

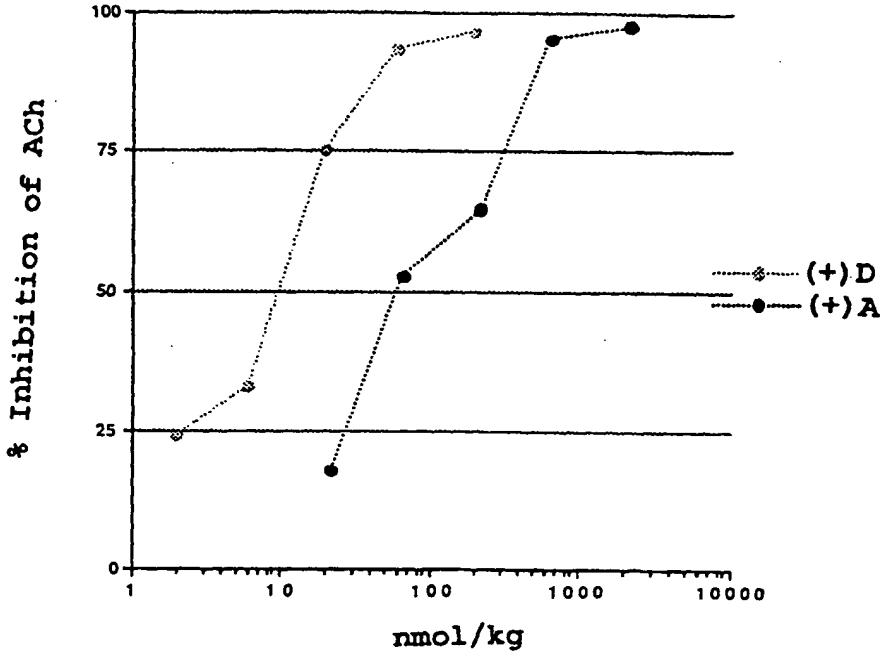


FIG. 1

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

(11) EP 1 019 358 B1

(12) **EUROPEAN PATENT SPECIFICATION**

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

(21) Application number: **98912864.0**

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

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

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

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

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

3,3-DIARYLPROPYLAMINE , IHRE VERWENDUNG UND HERSTELLUNG

3,3-DIARYLPROPYLAMINES, LEUR UTILISATION ET LEUR PREPARATION

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

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

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

(73) Proprietor: **Pharmacia AB**
112 87 Stockholm (SE)

(72) Inventors:
- **JOHANSSON, Rolf**
  S-141 38 Huddinge (SE)
- **HARALDSSON, Martin**
  S-183 72 Täby (SE)
- **RINGBERG, Erik**
  S-754 26 Uppsala (SE)
- **VAGBERG, Jan**
  S-192 71 Sollentuna (SE)
- **BEIERLEIN, Katarina**
  S-753 35 Uppsala (SE)
- **EMOND, Rikard**
  S-133 43 Saltsjöbaden (SE)
- **SJÖBERG, Birger**
  S-191 46 Sollentuna (SE)

(74) Representative: **Tannerfeldt, Sigrid Agneta et al**
Pharmacia AB
Patent Department
112 87 Stockholm (SE)

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

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

Printed by Jouve, 75001 PARIS (FR)

EP 1 019 358 B1

Description

TECHNICAL FIELD

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

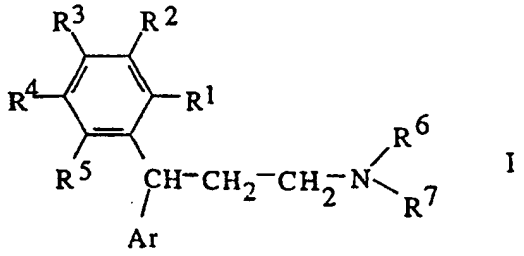
BACKGROUND OF THE INVENTION

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

SUMMARY OF THE INVENTION

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

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



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,
R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,
R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl of at least two carbon atoms, alkoxy of at least two carbon atoms, hydroxyalkyl of at least two carbon atoms,
R^5 is hydrogen, halogen, alkyl,
Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and
R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen,

with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or
(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or
(iii) Ar is heteroaryl, or

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[0029] R^5 is preferably hydrogen.

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

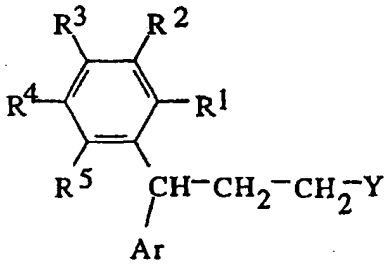
[0031] Exemplary groups $-NR^6,R^7$ are diethylamino, diisopropylamino, methyl-tert.-butylamino, methyl-tert.-pentylamino, piperidino, 2,2,6,6-tetramethylpiperidino, methylcyclobutylamino, methylcyclopentylamino, methylcyclohexylamino, methylcycloheptylamino, pyrrolidino, 2,2,5,5-tetramethylpyrrolidino,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

[0032] Representative compounds of Formula I are:

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

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

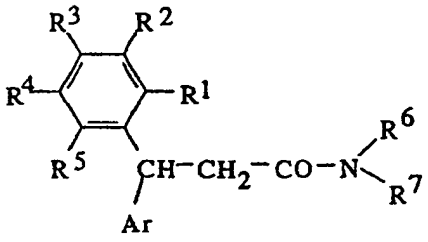
a) reacting a compound of Formula II



II

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

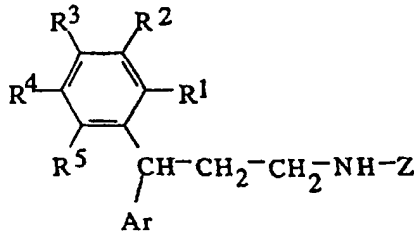
b) reducing a compound of Formula III



III

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

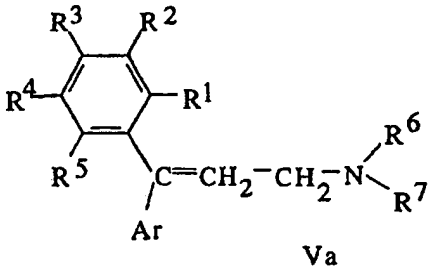
c) N-alkylating a secondary amine of Formula IV



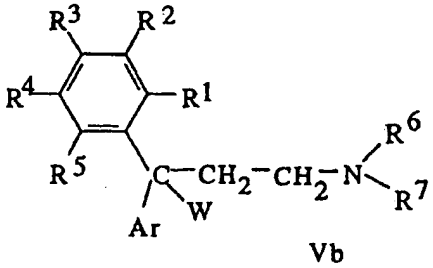
IV

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

d) reducing a compound of Formula Va or Vb



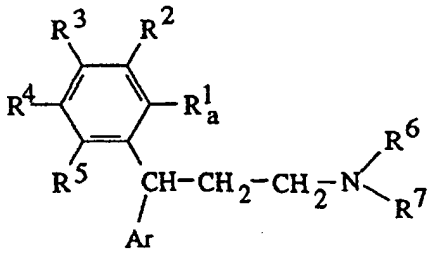
Va



Vb

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

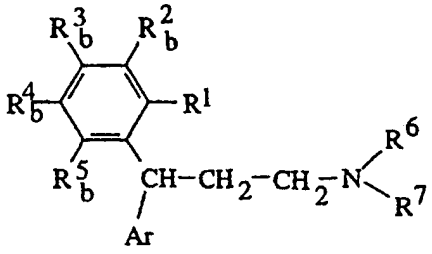
e) in a compound of Formula VI



VI

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

f) in a compound of Formula VII

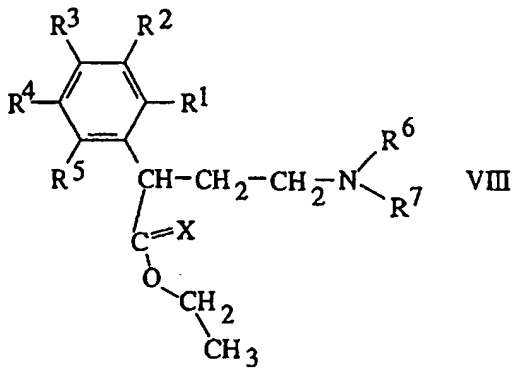


VII

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

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

h) reacting a compound of Formula VIII

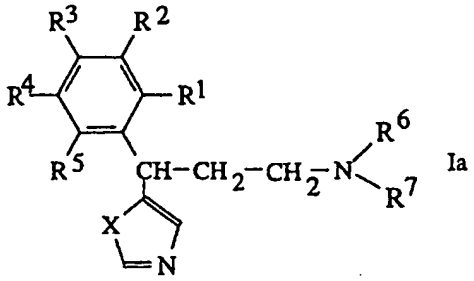


VIII

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

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

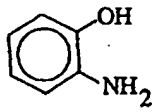
to form a compound of Formula Ia



Ia

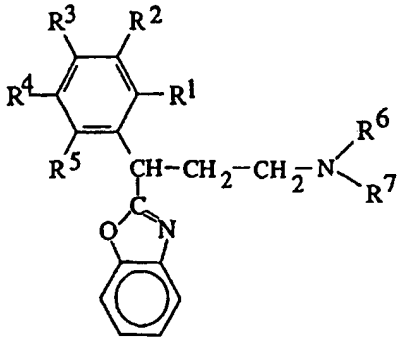
wherein R^1 to R^7 and X are as defined above, or

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



X

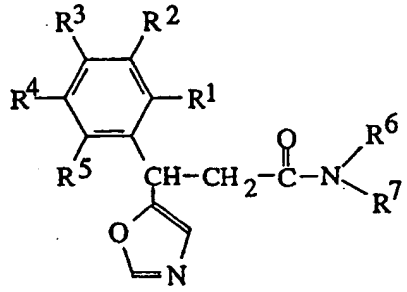
to form a compound of Formula Ib



Ib

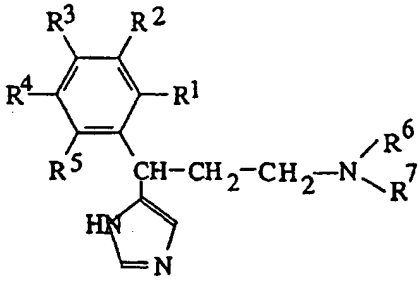
wherein R^1 to R^7 are as defined above for Formula I, or

j) converting a compound of Formula XI



XI

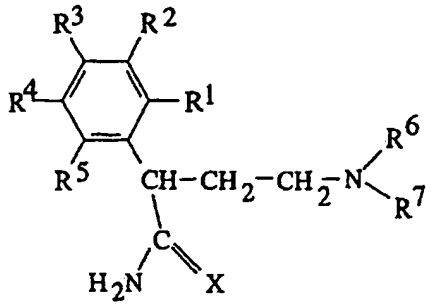
wherein R^1 to R^7 are as defined above for Formula I, to a compound of Formula XII



XII

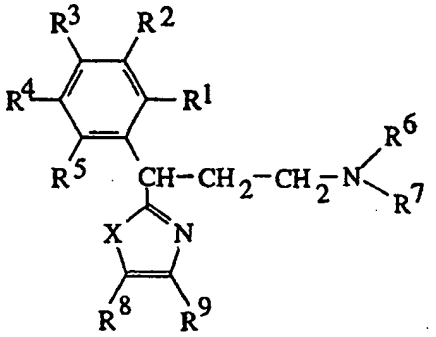
wherein R^1 to R^7 are as defined above for Formula I, or

k) converting a compound of Formula XIII



XIII

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



XIV

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

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

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

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

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

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

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

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

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

General

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

EXAMPLE 1

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

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

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

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

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

1.2 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0044] A solution of DCC (5.2 g, 17 mmol) in THF (20 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (6.9 g, 20 mmol), 2-(2-isopropylaminoethoxy)-ethanol, triethylamine (2.5 g, 25 mmol) and hydroxysuccinimide (2.8 g, 24 mmol) in THF (50 mL). The reaction mixture was stirred for 20 h. The solvent was evaporated and the residue chromatographed on silica (gradient from toluene to ethyl acetate). Yield 5.9 g (62%).

1.3 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

[0045] A solution of trans-N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3- (2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (5.9 g, 12 mmol) in acetic acid (50 mL) was hydrogenatated over Pd/C (10 %, 0.5 g) for 16 h. Filtering and evaporation of solvent left a residue that was chromatographed on silica (ethyl acetate). Yield 2.83 g (61 %).

EXAMPLE 2

N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

[0046] A solution of N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (0.93 g, 2.5 mmol)

in THF (20 mL) was added to LAH (0.22 g, 5.6 mmol) and the mixture was stirred at reflux temperature for 30 min. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (chloroform-methanol 9:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.45 g (46%); mp. 230-232°C. ^{1}H NMR (DMSO-d6) δ 1.27-1.70 (m, 10H), 1.88 (br, 1H), 2.05 (d, 1H), 2.17 (s, 3H), 2.42 (br, 1H), 2.60 (s, 3H), 2.85 (br, 2H), 3.34 (m, 1H), 4.30 (t, 1H), 6.72 (d, 1H), 6.80 (dd, 1H), 7.05 (br, 1H), 7.15 (t, 1H), 7.27 (t, 2H), 7.31 (d, 2H), 9.31 (s, 1H) and 10.53 (br, 1H). Anal. ($C_{24}H_{33}NO \cdot HCl$) C, H, N.

[0047] The starting compound N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

2.1 N-Cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0048] A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g, 20 mmol), cycloheptylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at room temperature. Another portion of cycloheptylamine (1.3 g) was added and the reaction mixture was left stirring for another 1 h. The mixture was filtered and the filtrate evaporated. The residue was dissolved in diethyl ether and washed with hydrochloric acid (1M), water and brine in subsequent order. After evaporation of the solvent, the residue was crystallised from toluene-hexane to give 7.3 g (83%). ^{1}H NMR ($CDCl_3$) δ 1.06 (br, 2H), 1.25-1.74 (m, 10H), 2.30 (s, 3H), 3.83 (m, 1H), 4.95 (s, 2H), 5.50 (d, 1H), 6.49 (s, 1H), 6.90-7.08 (m, 4H), and 7.12-7.44 (m, 9H).

2.2 N-Cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0049] A solution of N-cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.4 g, 10 mmol) and methyliodide (4 g, 30 mmol) in DMF (10 mL) was added to sodiumhydride (80 %, 1.2 g, 40 mmol) at ambient temperature and the mixture was stirred for 60 min. Excess sodium hydride was destroyed by adding methanol, and the reaction mixture was then partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallised from toluene-hexane to yield 4.4 g (97%). ^{1}H NMR ($CDCl_3$) (almost 1:1 mixture of rotameres) δ 1.20-1.80 (m, 12H), 2.30 (m, 3H) 2.61 (s, 1.5H), 2.71 (s, 1.5H), 3.93 (m, 0.5H), 4.46 (m, 0.5H), 4.81 (m, 1H), 6.43 (m, 1H), 6.81 (m, 2H) and 7.08-7.35 (m, 10H).

2.3 N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

[0050] A solution of N-cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (3.15 g, 7 mmol) in acetic acid (40 mL) was hydrogenated over Pd/C (10%, 0.2 g) for 72 h. The reaction mixture was filtered and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 0.95 g (37%). ^{1}H NMR ($CDCl_3$) δ 1.26-1.98 (m, 12H), 2.02 (s, 3H), 2.12 (s, 3H), 2.28 (m, 1H), 2.52 (m, 1H), 2.71 (m, 1H), 4.36 (dd, 1H), 6.39 (s, 1H), 6.76 (s, 2H), 7.15 (m, 2H) and 7.25 (m, 5H).

EXAMPLE 3

N-Cyclohexyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

[0051] A solution of N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.0 g, 9 mmol) in THF (90 mL) was added to LAH (0.50 g, 13 mmol) in THF (5 mL) and the mixture was stirred at ambient temperature for 2.5 h. The reaction was quenched and the solvent evaporated. The resulting oil was hydrogenated over Pd/C (10%, 1g) in acetic acid (70 mL) for 20 h. After filtration and evaporation of the solvent, the residue was chromatographed on silica (chloroform:methanol 99:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 1.2 g (36%); mp. 179-183°C. ^{1}H NMR (DMSO-d6) δ 1.05 (m, 1H), 1.21-1.38 (m, 4H), 1.51 (d, 1H), 1.74 (br, 2H), 1.86 (br, 1H), 2.00 (d, 1H), 2.17 and 2.19 (s, 3H), 2.39-2.56 (m, 2H), 2.63 (m, 3H), 2.82 (m, 1H), 2.93 (m, 1H), 3.17 (m, 1H), 4.32 (q, 1H), 6.73 and 6.75 (d, 1H), 6.79 and 6.81 (t, 1H), 7.02 and 7.10 (d, 1H), 7.14-7.18 (m, 1H), 7.25-7.29 (m, 2H), 7.33 (t, 2H), 9.34 (br, 1H) and 10.78 (s, 1H). Anal. ($C_{23}H_{31}NO \cdot HCl$) C, H, N.

[0052] The starting compound N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl) -3-phenylpropenamide was prepared as follows:

3.1 N-Cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

[0053] A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-meth-

ylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g, 20 mmol), N-methyl-cyclohexylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 2 h. A second portion of DCC (2.5 g, 13 mmol) and N-methyl-cyclohexylamine (1.5 g, 13 mmol) was added and the reaction mixture was left stirring for 16 h. Diethyl ether and hydrochloric acid (1M) were added and the organic phase was washed with brine. The organic layer was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 5.5 g (63%). ^{1}H NMR (DMSO-d6) (almost 1:1 mixture of rotameres) δ 0.88-1.06 (m, 2H), 1.16-1.39 (m, 5H), 1.55 (t, 2H), 1.67 (br, 1H), 2.21 (s, 1.5H), 2.23 (s, 1.5H) 2.56 (s, 1.5H), 2.67 (s, 1.5H), 3.67 (m, 0.5H), 4.05 (m, 0.5H), 4.82 (s, 1H), 4.85 (s, 1H), 6.57 (s, 0.5H), 6.59 (s, 0.5H), 6.84 (dd, 1H), 6.87 (d, 0.5H), 6.89 (t, 1H), 6.95 (dd, 1H), 6.98 (d, 0.5H), 7.12 (dd, 1H), 7.17 (m, 3H), 7.27 (m, 2H), and 7.32 (m, 3H).

EXAMPLE 4

N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamine hydrochloride

[0054] Boran·SMe_2-complex in THF (7 mL, 14 mmol) was gently refluxed with a weak stream of nitrogen for 30 minutes. N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide (1.55 g, 4.2 mmol) was added to the refluxing solution and the reflux was continued for 1 h. The reaction mixture was partioned between diethyl ether and sodium hydroxide (1M). The solvent of organic layer was evaporated and the residue was chromatographed on silica (toluene-triethylamine 9:1) to yield the free amine. The hydrochloride salt was obtained by dissolving the amine in diethyl ether with the addition of hydrogen chloride in diethyl ether. The resulting oil produced crystals after some time stirring in diethyl ether. Yield 0.39 g (23%); mp. 143-144°C. ^{1}H NMR (DMSO-d6) δ 1.19 (q, 6H), 1.25 (dd, 6H), 2.53 (m, 1H), 2.70 (m, 1H), 2.87 (m, 2H), 3.59 (m, 2H), 4.38 (t, 1H), 7.24 (t, 1H), 7.35 (t, 2H), 7.39 (d, 2H), 7,45 (t, 1H), 7.68 (t, 1H), 7.74 (t, 2H) and 10.25 (br, 1H). Anal. ($C_{22}H_{28}NF_3$·HCl) C, H, N.

[0055] The starting compound N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide was prepared as follows:

4.1 Diethyl N,N-diisopropylacetamide phosphonate

[0056] A mixture of triethylphosphite (23 g, 0.14 mol) and N,N-diisopropyl 2-bromoacetamide (29 g, 0.13 mol) was heated to 110°C for 3 h to yield 35 g (97%). The product was used without purification.

4.2 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide

[0057] A solution of diethyl N,N-diisopropylacetamide phosphonate (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 29 mmol) during 30 min, keeping the temperature below 30°C. A solution of 2-trifluoromethyl-benzophenone (5.0 g, 20 mmol) in THF (20 mL) was added and the reaction mixture was heated to 50°C and kept at that temperature for 16 h. A second portion of the phosphorous ylide (15 mmol), prepared as above, was added. After another 24 h at 50°C the mixture was partioned between diethyl ether and water. The etheral layer was evaporated and the residue chromatographed on silica (toluene-ethyl acetate 9:1) yielding 3.0 g (41%) as a mixture of the E- and Z-isomers. Labels a and b refer to the different isomers. ^{1}H NMR ($CDCl_3$-d) δ 0.80 (d, 6Ha), 1.08 (d, 3Hb), 1.24 (t, 6Hb), 1.31 (d, 3Hb), 1.44 (d, 6Ha), 3.32 (m, 1Ha), 3.34 (m, 1Hb), 4.19 (m, 1Hb), 4.32 (m, 1Ha), 6.04 (s, 1Ha), 6.65 (s, 1Hb) and 7.18-7.75 (m, 9Ha, 9Hb).

4.3 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide

[0058] A solution of N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide (2.95 g, 8.1 mmol) in ethanol (50 mL) was hydrogenated over Pd/C (10%, 300 mg) at normal pressure for 24 h. The catalyst was filtered off, the solvent partly evaporated and the product collected after crystallisation. Yield 1.78 g (60%). ^{1}H NMR ($CDCl_3$-d) δ 1.16 (m, 6H), 1.30 (m, 6H), 2.86 (dd, 1H), 3.11 (dd, 1H), 3.41 (m, 1H), 4.03 (m, 1H), 5.12 (m, 1H) and 7.10-7.78 (m, 9H).

EXAMPLE 5

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(3-pyridyl)-propanamine dihydrochloride

[0059] A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide (2.8 g, 8 mmol) in THF (25 mL) was added to LAH (1.3 g, 32 mmol). The reaction mixture was refluxed for 4 h whereafter the reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 99:1) to give 2.2 g. The product (1.3 g, 4 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to -78°C and boron

tribromide (1 g, 8 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature during 1 h. The reaction mixture was washed with sodium hydroxide (1M) and brine and the organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 9:1) to give 0.35 g. The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to produce the dihydrochloride as crystals which soon rearranged to a hard glass. ^{1}H NMR (DMSO-d6) δ 1.22 (dd, 6H), 1.28 (dd, 6H), 2.60 (m, 1H), 2.70 (m, 1H), 2.93 (m, 2H), 3.60 (m, 2H), 4.60 (t, 1H), 6.85 (t, 1H), 6.89 (d, 1), 7.11 (t, 1H), 7.38 (d, 1H), 7.96 (dd, 1H), 8.46 (d, 1H), 8.75 (d, 1H), 8.85 (s, 1H), 9.90 (br, 1H) and 10.14 (s, 1H).

[0060] The starting compound N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide was prepared as follows:

5.1 2-Methoxyphenyl-3-pyridyl-ketone

[0061] A solution of 2-bromoanisole (21 g, 0.11 mol) in diethyl ether (100 mL) was added to magnesium turnings during 45 minutes with heating. After the addition the reflux was continued for 15 min. The Grignard reagent was cooled to 0°C and a solution of 3-cyanopyridine (10 g, 0.10 mol) in diethyl ether (100 mL) was added dropwise. The mixture was refluxed for a few minutes. Hydrochloric acid (20 mL, 0.24 mol, conc.) and 2-propanol (20 mL) were added and the reflux was continued for 30 min. Water and diethyl ether were added and the phases separated. The water-phase was made alkaline (2M NaOH) and was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated to yield 17 g. The crude was chromatographed on silica (toluene-ethyl acetate 19:1) to give 3.75 g (19%). ^{1}H NMR ($CDCl_3$-d) δ 3.76 (s, 3H), 7.01 (d, 1H), 7.10 (t, 1H), 7.41 (dd, 1H), 7.46 (dd, 1H), 4.53 (m, 1H), 8.12 (d, 1H), 8.75 (s, 1H) and 8.94 (s,

5.2 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide

[0062] A solution of of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (9.3 g, 33 mmol) in THF (40 mL) was added dropwise to sodium hydride (80 %, 1.0 g, 33 mmol) during 15 min. The mixture was heated to 40°C for 15 minutes and then cooled to 5°C whereafter a solution of 2-methoxyphenyl-3-pyridyl-ketone (4.5 g, 21 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 16 h. The reaction mixture was partioned between diethyl ether and water and the organic phase was dried ($MgSO_4$) and evaporated to yield 7.1 g of solid material. The product was hydrogenated over Pd/C (10%, 0.2 g) in acetic acid (50 mL) for 48 h. The reaction mixture was filtered and the solvent evaporated. The residue was partioned between diethyl ether and hydrochloric acid (1 M) and the phases were separated. The water-phase was made alkaline (2 M sodium hydroxide) and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and filtered. Crystallisation began and the mixture was diluted with hexane. Filtration gave 2.9 g (40%). ^{1}H NMR ($CDCl_3$-d) δ 1.14 (dd, 6H), 1.28 (d, 6H), 3.04 (dd, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.05 (m, 1H), 5.00 (t, 1H), 6.84 (d, 1H), 6.92 (t, 1H), 7.19 (m, 3H), 7.57 (d, 1H), 8.39 (m, 1 H) and 8.55 (d, 1H). 1H).

EXAMPLE 6

N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

[0063] A solution of N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide (3.1 g, 9.4 mmol) in THF (20 mL) was added to LAH (1.0 g, 25 mmol) and the reaction mixture was stirred at reflux temperature for 2 h. More LAH (0.5 g), was added and the reflux continued for another 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 3:1) to give 0.4 g of the free amine as a syrup. The amine was dissolved in isopropanol/diethyl ether and hydrogen chloride in diethyl ether was added to give the amine salt. Yield 0.32 g (10 %); mp 152-154 °C. ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.26 (dd, 6H), 2.57 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.36 (t, 1H), 6.69 (dd, 1H), 7.14 (m, 1H), 7.22 (m, 2H), 7.29 (m, 1H), 7.32 (d, 2H), 7.33 (s, 2H), 7.54 (m, 1H) and 10.24 (br, 1H). Anal. ($C_{21}H_{28}NF$·HCl) H, N; C: calcd, 72.1; found, 72.6.

[0064] The starting compound N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide was prepared as follows:

6.1 trans-N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide

[0065] A solution of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 25 mmol) during 30 min, keeping the temperature below 40°C. A solution of 2-trifluoromethyl-benzophenone (4.0 g, 20 mmol) in THF (10 mL) was added and the reaction mixture was stirred at ambient temperature for 30 min. The mixture was partioned between diethyl ether and brine. The organic layer was dried ($MgSO_4$) and evaporated to give a crystalline mass. Recrystallisation from hexane yielded 3.9 g (60

%). ^{1}H NMR ($CDCl_3$-d) δ 0.85 (d, 6H), 1.39 (d, 6H), 3.29 (m, 1H), 4.27 (m, 1H), 6.29 (s, 1H), 7.10 (m, 3H) and 7.30 (m, 6H).

6.2 N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide

[0066] A solution of trans-N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide (3.25 g, 10 mmol) was hydrogenated over Pd/C (10%, 300 mg) in acetic acid (30 mL) for 24 h. The catalyst was filtered off and the solvent was evaporated to yield 3.15 g (96%). ^{1}H NMR ($CDCl_3$-d) δ 1.12 (q, 6H), 1.28 (q, 6H), 3.05 (d, 2H), 3.38 (m, 1H), 4.03 (m, 1H), 4.93 (t, 1H) and 6.94-7.32 (m, 9H).

EXAMPLE 7

(R) -N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0067] Hydrogen chloride in diethyl ether was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (0.81 g, 2.4 mmol) in diethyl ether and 2-propanol. Crystals were filtered to yield 0.4 g (45%); mp 178-179°C. $[\alpha]_{Hg}$ = -40° (c 1.1 in methanol) . ^{1}H NMR (DMSO-d6) δ 1.16 (d, 3H), 1.20 (d, 3H), 1.24 (d, 3H), 1.27 (d, 3H), 2.54 (m, 2H), 2.84 (m, 1H), 2.97 (m, 1H), 3.58 (br, 2H), 4.38 (t, 1H), 7.08 (d, 1H), 7.22 (t, 1H), 7.32 (m,4H), 7.65 (dd, 1H), 7.83 (d, 1H), 9.80 (s, 1H), 9.86 (br, 1H) 10.99 (s, 1H). Anal. ($C_{22}H_{29}NO_2$·HCl) H, N; C: calcd, 70.3; found, 70.8.

[0068] The starting compound (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine was prepared as follows:

7.1 (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine

[0069] DDQ (1.1 eq) was added to a solution of (R)-N,N-diisopropyl-3- (2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine mandelate (prepared as described in WO 94/11337, Example 1) (2.46 g, 5 mmol), dichloromethane (20 mL) and phosphate buffer (pH 7) (0.1 mL). Thereafter, sodium hydroxide solution (20 mL, 1 M) and diethyl ether were added and the phases were separated. The water-phase was extracted twice with dichloromethane-diethyl ether (2:1). The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate-hexane to yield 1.35 g (80 %).

EXAMPLE 8

(R)-N,N-Diisopropyl-3-[5-(7-hydroxy-2-aza-5-oxaheptyl)-2-hydroxyphenyl]-3-phenylpropanamine di-(S)-mandelate

[0070] Sodiumcyanoborohydride (0.25 g, 3.9 mmol) was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (Example 7.1), (1.25 g, 3.7 mmol) and 2-ethoxy-(2-amino)-ethanol (19.5 g, 18 mmol) in methanol (10 mL). Hydrochloric acid (conc) was added to adjust pH to about 3. After 3h, the pH was adjusted to about 1 and the solvent was evaporated. The residue was partioned between diethyl ether and water, whereafter the organic layer was evaporated and the residue chromatographed on silica (chloroform-triethylamine-methanol 88: 10:2). The pure amine was dissolved in 2-propanol-diethyl ether with (S)-mandelic acid (2 eq), whereby the product crystallised (the crystals were unstable and an oily mass was soon obtained). Yield 0.2 g (7%); mp dec. ^{1}H NMR (free amine) ($CDCl_3$-d) δ 1.05 (d, 6H), 1.09 (d, 6H), 2.10 (m, 1H), 2.35 (m, 2H), 2.67 (m, 3H), 3.19 (m, 2H), 3.47 (m, 2H), 3.49 (t, 2H), 3.56 (d, 2H), 3.63 (t, 2H), 4.45 (dd, 1H), 6.75 (d, 1H), 6.79 (d, 1H), 6.95 (dd, 1H), 7.18 (m, 1H) and 7.26-7.33 (m, 4H).

EXAMPLE 9

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine hydrochloride

[0071] A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (0.92 g, 2 mmol) in ethanol (30 mL) was hydrogenated over Pd/C (10%, 50 mg) at room temperature for 2 h. The catalyst was filtered off and the solution was treated with hydrogen chloride to obtain the amine salt. Yield 0.66 g (81 %); mp 177-178°C; $[\alpha]_D$ = -23° (c 1.0, methanol). ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.25 (dd, 6H), 2.48 (m, 2H), 2.85 (m, 1H), 2.95 (m, 1H), 3.58 (m, 2H), 3.78 (s, 3H), 4.38 (t, 1H), 6.98 (d, 1H), 7.20 (m, 1H), 7.31 (d, 2H), 7,32 (s, 2H), 7.69 (dd, 1H), 7.81 (d, 1H), 9.85 (br, 1H), 10.74 (s, 1H). Anal.

($C_{23}H_{31}NO_3$·HCl) H, N, C.

EXAMPLE 10

N,N-Diisopropyl-3-(2-hydroxymethyl)phenyl-3-phenylpropanamine hydrochloride

[0072] A solution of N,N-diisopropyl-3-(2-carboxyphenyl)-3-phenylpropanamine hydrochloride (1.88 g, 5 mmol) in THF (30 mL) was added to LAH (1.5 g, 38 mmol) and the reaction mixture was stirred att ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was dissolved in hot diethyl ether-2-propanol (100 mL, 1:4), whereafter HCl in diethyl ether was added. After cooling the product was filtered and dried at 60°C (vacuum). Yield 1.2 g (68%); mp 223-224°C. ^{1}H NMR (DMSO-d6) δ 1.18 (t, 6H), 1.25 (q, 6H), 2.91 (m, 2H), 3.26 (disturbed by solvent, 2H), 3.57 (m, 2H), 4.38 (t, 1H), 4.43 (d, 1H), 4.74 (d, 1H), 5.22 (s, 1H), 7.20 (q, 2H), 7.25-7.35 (m, 5H), 7.40 (dd, 2H), 9.95 (s, 1H). Anal. ($C_{22}H_{31}NO$·HCl) H, N, C.

EXAMPLE 11

(S)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

[0073] (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (0.67 g, 1.5 mmol) was hydrogenated over Pd/C (10%, 67 mg) at atmospheric pressure overnight in ethanol (20 mL). The catalyst was filtered off and the solvent was evaporated. The residue was partioned between diethyl ether and sodium hydroxide (1 M). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The amine salt was obtained by dissolving the amine in diethyl ether-isopropanol and treatment with hydrogen chloride in diethyleter. Yield 0.37 g; mp 219-221 °C; $[\alpha]_D$ -11.4° (c=1.0, methanol); ^{1}H NMR (CD_3OD) δ 1.30 (d, 12H), 2.36-2.60 (m, 2H), 2.68 (t, 2H), 3.05 (t, 2H), 3.60-3.72 (m, 4H), 4.40 (t, 1H), 6.73 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.17-7.38 (m, 5H). Anal. ($C_{23}H_{33}NO_2$·HCl·0.2H_2O) C, H, N.

[0074] The starting compound (S)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxy)ethylphenyl]-3-phenylpropanamine was prepared as follows:

11.1 (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

[0075] A mixture of (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8 g, 12.7 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), tri-o-tolyl-phosphine (74 mg, 0.14 mmol) and tributylamine (5.9 mL, 24.5 mmol) in dimethylacetamide (50 mL) was heated to 60 °C under nitrogen atmosphere. Ethene (g) was then added to 8 bars pressure. After stirring overnight the reaction mixture was allowed to cool to room temperature. Nitrogen was flushed through the reaction vessel, and toluene and water were added. The aqueous layer was extracted with toluene and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was treated with sodium hydroxide (1 M) and extracted with diethyl ether and toluene. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica (gradient ethyl acetate-methanol 90:10 up to 0.06% NH_3 in ethyl acetate-methanol 90:10) Yield 1 g (18%); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

11.2 (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0076] (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (1 g, 2.34 mmol) in THF (25 mL) was added to 9-BBN (0.5 M in THF, 11.7 mL, 5.85 mmol) under nitrogen atmosphere at 0 °C. Additional 9-BBN (2.3 mL, 1.2 mmol) was added after 3 hours of stirring, the temperature was raised to room temperature and the mixture was stirred for 0.5 hour. It was then cooled to 0 °C and 1 M sodium hydroxide (10 mL) was added followed by H_2O_2 (30% in H_2O, 10 mL). After 1 hours stirring, water was added and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (gradient of diethyl ether to 1% NH_3 in diethyl ether). Yield 0.67 g (64%). ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 12H), 2.10-2.18 (m, 2H), 2.30-2.37 (m, 2H), 2.80 (t, 2H), 2.90-3.0 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 5.0 (s, 2H), 6.80 (d, 1H), 7.0 (m, 1H), 7.10-7.38 (m, 11H).

EXAMPLE 12

(R)-N,N-Diisopropyl-3- [2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

[0077] The title compound as well as the starting compounds were prepared in an analogous manner to the preparation described in Example 11, with the exception that (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was changed to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1).

Yield 0.35 g (33%); mp 209-215 °C; $[\alpha]_D$ +9.8° (c=1.0, methanol); ^{1}H NMR (CD_3OD) δ 1.29 (d, 12H), 2.40-2.60 (m, 2H), 2.67 (t, 2H), 3.04 (t, 2H), 3.61-3.72 (m, 4H), 4.40 (t, 1H), 6.70 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.18-7.40 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

[0078] Preparation of starting compounds:

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

[0079] Yield 5.5 g (53%); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

12.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0080] Yield 1.2 g (75%); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 12H), 2.15 (m, 2H), 2.32 (m, 2H), 2.80 (t, 2H), 2.95 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 4.98 (s, 2H), 6.80 (d, 1H), 6.96 (m, 1H), 7.10-7.35 (m, 11H).

EXAMPLE 13

(R)-N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0081] (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine (1 g, 2.25 mmol) was treated as described in Example 11. Yield 0.6 g (68%); mp 105-115 °C; $[\alpha]_D$ -32.6° (c 1.02, methanol); ^{1}H NMR (DMSO-d_6) d 1.18-1.28 (m, 12H), 2.5 (m, 3H), 2.50-2.62 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.38 (t, 1H), 6.99 (d, 1H), 7.2 (m, 1H), 7.29-7.35 (m, 4H), 7.73 (dd, 1H), 7.85 (d, 1H), 9.90 (br, 1H), 10.70 (s, 1H). Anal. ($C_{23}H_{31}NO_2 \cdot HCl \cdot 0.4H_2O$) C, H, N.

[0082] The starting compound (R)-N,N-diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

13.1 (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine

[0083] To a stirred solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (Example 12) (10.2 g, 21.23 mmol) in DMF (100 mL) under nitrogen atmosphere at room temperature were sequentially added triethylamine (2.58 g, 25.47 mmol), TlOAc (6.15 g, 23.35 mmol), isobutylvinylether (14 mL, 106.14 mmol), DPPP (0.87 g, 2.12 mmol) and $Pd(OAc)_2$ (0.24 g, 1.06 mmol). The reaction temperature was raised to 100 °C and stirred for 3 hours, cooled to room temperature, filtered and treated with HCl (5%, 250 mL) and stirred for another 2 hours. The reaction mixture was repeatedly extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. Triethylamine and DMF were destilled off under reduced pressure to yield 9 g (98%); ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 12H), 2.52-2.70 (m, 7H), 3.40 (br, 2H), 4.34 (t, 1H), 5.10 (s, 1H), 6.90 (d, 1H), 7.17-7.40 (m, 10H), 7.82 (m, 1H) and 7.92 (s, 1H).

EXAMPLE 14

N,N-Diisopropyl-3(R)-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine fumarate

[0084] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine (2.7 g, 6.05 mmol) was hydrogenated over Pd/C (0.27 g, 10%) in ethanol at atmospheric pressure for 2 hours. The catalyst was filtered off and the solvent was evaporated. The resulting oil was chromatographed on silica (toluene-triethylamine 90:10). Fumarate salt of the amine was afforded by adding fumaric acid (0.13 g, 1.13 mmol) dissolved in warm ethanol to a solution of the free base in diethyl ether yielding white crystals (0.44 g, 83%); mp 240-244 °C; $[\alpha]_D$ +9.8° (c 1.02, methanol); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.26 (dd, 3H), 2.20-2.30 (m, 2H), 2.55-2.67 (m, 2H), 3.30 (m, 2H), 4.32 (t, 1H), 4.59 (q, 1H), 6.53 (s, 2H), 6.72 (dd, 1H), 6.93 (dd, 0.5H), 7.12-7.17 (m, 1H), 7.21-7.31 (m, 5H). Anal.

($C_{23}H_{33}NO_2 \cdot C_4H_4O_4 \cdot 0.3H_2O$) C, H, N.

[0085] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

14.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine

[0086] N,N-Diisopropyl-3(R)-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine, prepared as described in Example 13.1, (3.5 g, 7.90 mmol) dissolved in dry THF was added to $LiAlH_4$ (0.2 g, 5.41 mmol). After 2 hours of stirring, additional $LiAlH_4$ (50 mg, 1.32 mmol) was added and the reaction mixture was stirred for 1.5 hours. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-E_3N 90:10) to give 2.74 g (78%) of an oil that crystallised slowly upon storage at room temperature.

EXAMPLE 15

(+)-N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine fumarate

[0087] N,N-Diisopropyl-3(R)-[2-benzyloxy 5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (0.55 g, 1.2 mmol) was treated in an analogous manner to that described in Example 14 above, which yielded white crystals, 0.32 g (55%); mp 196-200 °C; $[\alpha]_D$ +13.5° (c 1.0, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.40-2.48 (m, 1H), 2.52-2.60 (m, 1H), 3.03 (t, 2H), 3.55 (d, 2H), 3.66 (m, 2H), 4.42 (t, 1H), 4.57 (t, 1H), 6.7 (s, 2H), 6.79 (d, 1H), 7.05 (dd, 1H), 7.16-7.21 (m, 2H), 7.28 (m, 2H), 7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3$-$C_4H_4O_4$) C, H, N.

[0088] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

15.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine

[0089] To an ice-chilled solution of AD-mix-α (5.7 g) in H_2O (20 mL) and t-BuOH (10 mL) was added N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (Example 12.1), (1.74 g, 4.1 mmol) dissolved in t-BuOH (10 mL). After 1 hour of stirring, the ice bath was removed and the reaction mixture was stirred for additional 21 hours. Na_2SO_3 (6 g) was then added and after 1 hours of stirring the reaction mixture was partioned between H_2O and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine, 90:10) to afford 0.55 g. ^1H NMR ($CDCl_3$) δ 0.9 (s, 6H), 0.95 (s, 6H), 2.15-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.96 (m, 2H), 3.60-3.70 (m, 2H), 4.41 (t, 1H), 4.75 (m, 1H), 5.0 (s, 2H), 6.85 (d, 1H), 7.10-7.35 (m, 12H).

EXAMPLE 16

(-)-N,N-Diisopropyl-3(R)-[5-(1(S*),2-dihydroxyethyl) 2-hydroxyphenyl]-3-phenylpropanamine fumarate

[0090] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (1.1 g, 2.4 mmol) was treated in an analogous manner to that described in Example 11 which yielded white crystals, 0.25 g (21%); mp 208-211 °C; $[\alpha]_D$ -8° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.39-2.47 (m, 1H), 2.51-2.59 (m, 1H), 3.03 (t, 2H), 3.51-3.53 (m, 2H), 3.67 (m, 2H), 4.42 (t, 1H), 4.54 (dd, 1H), 6.68 (s, 2H), 6.78 (d, 1H), 7.06 (dd, 1H), 7.16-7.20 (m, 2H), 7.26 (m, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

[0091] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was obtained by treating N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (obtained in Example 12.1) as described in Example 15.1 above, but with AD-mix-β replacing AD-mix-α. Yield 1.2 g (44%).

EXAMPLE 17

(R)-[N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine hydrochloride

[0092] N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine (0.35 g, 0.72 mmol) was treated in an analogous manner to that described in Example 14. Yield 0.10 g (31%); mp 147-156 °C; $[\alpha]_D$ +8.2° (c 1.01, methanol); ^1H NMR (CD_3OD) δ 1.25-1.32 (m, 16H), 1.45-1.54 (m, 4H), 2.40-2.48 (m, 3H), 2.51-2.59 (m, 1H), 3.0-3.10 (m, 2H), 3.51 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.72 (d, 1H), 6.86 (dd, 1H), 6.91 (d, 1H), 7.19 (m, 1H), 7.30 (t, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{27}H_{41}NO_2 \cdot HCl \cdot 2H_2O$) C, N; H: calcd, 9.6; found, 8.3.

[0093] The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropan-

amine was prepared as follows:

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

[0094] n-BuLi (2.5 M in hexane, 19 mL, 47.5 mmol) was added to a solution of to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3- phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8.9 g, 18.52 mmol) in dry diethyl ether (100 mL) kept at -40 °C under nitrogen atmosphere. After 1.5 hour of stirring, additional n-BuLi (10 mL, 25 mmol) was added and after 2 hours another n-BuLi (5 mL, 12.5 mmol) was added. The reaction was then stirred for 15 minutes and DMF (6 mL, 77.8 mmol) was added followed by additional DMF (5 mL, 64.8 mmol) after 20 minutes of stirring. The temperature was allowed to rise to room temperature and after 35 minutes of stirring, NH_4Cl (sat.) was added followed by water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (toluene-triethylamine 90:10) to afford 8 g (100%) of a yellowish oil; ^1H NMR ($CDCl_3$) δ 0.90 (m, 12H), 2.12-2.40 (m, 4H), 2.95 (m, 2H), 4.44 (t, 1H), 5.10 (s, 2H), 6.95 (d, 1H), 7.15-7.36 (m, 10H), 7.70 (dd, 1H), 7.91 (s, 1H), 9.88 (s, 1H).

17.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy 5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine

[0095] To a slurry of 4-carboxybutyl triphenylphosphonium bromide (4.1 g, 9.31 mmol) in THF (25 mL) at -10 °C under nitrogen atmosphere was added potassium tert-butoxide (2.1 g, 18.62 mmol). The mixture turned orange and after 10 minutes stirring, (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine (2 g, 4.65 mmol) in THF (10 mL) was added. After 4 hours of stirring, hydrochloric acid (1M) and diethyl ether were added and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine 90:10 followed by methanol) to afford 3 g containing traces of triphenylphosphine. The product was used in the next step without further purification.

17.3 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine

[0096] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine was reduced as described in Example 10. Yield 0.35 g (15%).

EXAMPLE 18

(R)-N,N-Diisopropyl-3-[5-(2-diisopropylaminoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0097] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine (0.6 g, 1.13 mmol) was refluxed with concentrated HCl (25 mL) overnight. The reaction mixture was then basified with 10 M sodium hydroxide and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.5 g oil that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. The resulting diethyl ether solution was treated with hydrogen chloride in diethyl ether. Yield 50 mg (9%); $[\alpha]_D$ +1.4° (c 0.94, methanol); ^1H NMR (CD_3OD) δ 1.27-1.34 (m, 12H), 1.36-1.42 (m, 12H), 2.50-2.58 (m, 1H), 2.60-2.67 (m, 1H), 2.95 (t, 2H), 3.05 (m, 2H), 3.15-3.27 (m, 2H), 3.70 (m, 2H), 3.75 (m, 2H), 4.40 (t, 1H), 6.80 (d, 1H), 7.02 (dd, 1H), 7.13 (d, 1H), 7.20 (m, 1H), 7.31 (m, 1H), 7.39-7.41 (m, 1H). Anal. ($C_{29}H_{46}N_2O \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

[0098] The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine was prepared as follows:

18.1 N,N-Diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine

[0099] DMSO (1.1 mL, 15.5 mmol) dissolved in dichloromethane was added dropwise to oxalyl chloride (0.64 mL, 7.74 mmol) at -78 °C under nitrogen atmosphere. After 10 minutes of stirring, (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (Example 12.2) (2.3 g, 5.16 mmol) in dichloromethane was added and the reaction mixture was stirred for additional 1 h. Triethylamine (5.4 mL, 38.7 mmol) was then added and the temperature was allowed to rise to room temperature. The reaction mixture was taken up in water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the product was used in the next step without further purification.

18.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine

[0100] Diisopropylamine (4.2 mL, 30 mmol) was dissolved in methanol (12 mL). 5 M HCl in methanol (2 mL) was added followed by N,N-diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine (5 mmol) in methanol (10 mL) and sodium cyanoborohydride (0.22 g, 3.5 mmol). The reaction mixture was stirred at room temperature overnight. methanol was then evaporated, and diethyl ether and H_2O were added. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 3 g of a crude product that was chromatographed on silica (toluene-triethylamine 95:5). Yield 0.65 g (25%); ^1H NMR ($CDCl_3$) δ 0.88-0.91 (m, 18H), 1.20 (d, 9H), 2.10-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.87-3.10 (m, 4H), 4.34 (m, 1H), 4.98 (d, 2H), 6.75-6.97 (m, 2H), 7.10-7.30 (m, 11H).

EXAMPLE 19

(R)-N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine

[0101] (R)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (3.9 g, 11.5 mmol) and Al_2O_3 (115 g, 1.13 mol) refluxed in ethyl acetate (0.5 L) for 60 hours. Al_2O_3 was filtered off and ethyl acetate was evaporated. Chromatography on silica (toluene-triethylamine, 90:10) of the residue yielded 2.5 g (59%). The fumarate salt was obtained by adding fumaric acid (0.17 g, 1.48 mmol) dissolved in warm ethanol to the free base (0.55 g, 1.48 mmol) in diethyl ether; mp 174-177 °C; $[\alpha]_D$ +5.5° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.15 (t, 3H), 1.27-1.30 (m, 12H), 2.41-2.49 (m, 1H), 2.52-2.60 (m, 1H), 3.04 (dd, 2H), 3.49 (q, 2H), 3.67 (m, 2H), 4.35 (s, 2H), 4.43 (t, 1H), 6.69 (s, 2H), 6.80 (d, 1H), 7.04 (dd, 1H), 7.12 (d, 1H), 7.18-7.37 (m, 4H). Anal. ($C_{24}H_{35}NO_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 20

N-Isopropyl-3-(5-carboxy-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0102] N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine (1.3 g, 2.6 mmol) was dissolved in HOAc. Palladium (10%) on charcoal (0.13 g) was added and the mixture was hydrogenated at atmospheric pressure for 48 hours. The catalyst was then filtered off and the solvent was evaporated. The resulting oil was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). This purification was done in 16 portions with about 100 mg material each time. The pure fractions were pooled and freeze-dried to give 0.57 g of trifluoroacetic acid salt. The crystals were dissolved in 1 M HCl and freeze-dried to give 0.4 g (43%) of the hydrochloride salt as white crystals; mp 155-160 °C; ^1H NMR (DMSO-d_6) δ 1.17 (d, 3H), 1.19 (d, 3H), 2.30-2.38 (m, 1H), 2.38-2.46 (m, 1H), 2.72 (br, 1H), 2.80 (br, 1H), 3.25 (m, 1H), 4.40 (t, 1H), 6.94 (d, 1H), 7.18-7.22 (m, 1H), 7.29-7.33 (m, 4H), 7.66 (dd, 1H), 7.76 (d, 1H); Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

[0103] The starting compound N-benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine was prepared as follows:

20.1 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal

[0104] 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanol (16.5 g, 41.5 mmol) (prepared as described in WO 94/11337, Example 1c) was reacted as described in Example 18.1. The combined organic layers were washed with 2 M HCl, 10% $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated to give 16 g (98%) of yellowish crystals of the product that was used in the next step without further purification; mp 99-100 °C; ^1H NMR ($CDCl_3$) δ 3.10 (dd, 2H), 5.0 (s, 2H), 4.98-5.10 (m, 1H), 6.76 (d, 1H), 7.16-7.38 (m, 12H), 9.65 (s, 1H).

20.2 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0105] To a solution of N-benzylisopropylamine (34 mL, 0.20 mol) in methanol (80 mL) was added 5 M HCl in methanol (16.2 mL, 80.9 mmol) followed by 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (16.0 g, 40.5 mmol) in methanol (20 mL) and sodium cyanoborohydride (1.78 g, 28.3 mmol). The resulting solution was stirred for 17 hours. The solvent was evaporated and diethyl ether was added to the resulting syrup. The solution was washed 3 times with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (hexane-ethyl acetate, 75:25) giving 15.9 g of a syrup. The hydrochloride salt of the compound was prepared by dissolving the product in diethyl ether and adding HCl dissolved in diethyl ether. The resulting oil was washed with diethyl ether, dissolved in 10 M sodium hydroxide and extracted with diethyl ether 3 times. Purification by chromatography on silica (using a gradient of dichloromethane up

to 1% triethylamine in dichloromethane) yielded 7 g (33%) of the product as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H), 0.90 (d, 3H), 2.02-2.12 (m, 2H), 2.38 (t, 2H), 2.90 (m, 1H), 3.50 (d, 2H), 4.50 (t, 1H), 4.95 (s, 2H), 6.70 (s, 1H), 7.10-7.35 (m, 17H).

20.3 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine

[0106] A mixture of magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal) was warmed gently. A solution of N-benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (6.0 g, 11 mmol) and 1,2-dibromoethane (0.2 mL, 2.3 mmol) in dry THF (25 mL) was added dropwise under nitrogen atmosphere to the refluxing mixture. After 2 hours of refluxing, 1,2-dibromoethane (0.59 mL, 6.8 mmol) was added. The mixture was left overnight under nitrogen atmosphere. The mixture was then added together with 1,2-dibromoethane (0.93 mL, 10.8 mmol) to warmed magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal). After 30 minutes of refluxing, the mixture was cooled to room temperature and CO_2 (g) was bubbled through. After 3 hours, ammonium chloride (aq, 15%, 50 mL) was added followed by diethyl ether (100 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated to give 5.8 g of an oil. The crude product was chromatographed on silica (using a gradient of acetone up to 5% ethanol in acetone) to give the pure product (1.3 g, 23%) as an oil. N-benzyl-N-isopropyl-3-(2-benzyloxyphenyl)-3-phenylpropanamine (3.1 g) was obtained as a biproduct from the reaction. ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 3H), 1.10 (d, 3H), 2.30-2.40 (m, 2H), 2.46-2.65 (m, 2H), 3.40 (br, 1H), 3.85 (br, 2H), 4.30 (br, 1H), 4.98 (br, 2H), 6.80 (d, 1H), 7.10-7.40 (m, 15H), 7.95 (d, 1H), 7.95 (d, 1H), 8.20 (s, 1H).

EXAMPLE 21

N-Benzyl-N-isopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0107] N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine, prepared as described in Example 20.3, (3.1 g, 6.90 mmol) was refluxed in concentrated HCl (30 mL) for 20 h. The reaction mixture was allowed to cool to room temperature and the liquid was poured off. The remaining oil was washed with water and diethyl ether and then dissolved in 2-propanol. The solution was evaporated and treated with 10 M sodium hydroxide to give the free base. Chromatography on silica (hexane:ethyl acetate 75:25) afforded 0.5 g of the compound that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. To the resulting diethyl ether solution was added dropwise saturated diethyl ether-HCl (g). The resulting crystals of the hydrochloric salt were collected by filtration; mp 115-122 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 6H), 2.27-2.38 (m, 1H), 2.48-2.55 (m, 1H), 2.72-2.97 (m, 2H), 3.55 (m, 1H), 4.23 (m, 2H), 4.35 (m, 1H), 6.68-6.74 (m, 1H), 6.82 (dt, 1H), 6.96-7.24 (m, 7H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H), 9.55 (d, 1H), 10.62 (br, 1H). Anal. ($C_{25}H_{29}NO$·HCl) C, H, N.

EXAMPLE 22

(R)-N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine dihydrochloride

[0108] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine (3.20 g, 7.07 mmol) was dissolved in 100 % acetic acid and 10% Pd/C (0.52 g) was added. The mixture was hydrogenated (60 psi) overnight at room temperature. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in water, basified with sodium hydroxide (11 M), extracted with ethyl acetate, the organic phase was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (toluene-ethyl acetate-triethylamine-methanol, 20:5:1.5:1). The amine was redissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate was filtered off wich gave 0.30 g (10 %); ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 1.88 (m, 2H), 2.51(m, 2H), 2.59 (t, 2H), 2.88 (t, 2H), 3.04 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 4.55 (bs, 1H), 6.76 (d, 1H), 6.93 (d, 1H), 7.03 (s, 1H), 7.19 (t, 1H), 7.30 (t, 2H), 7.37 (d, 2H); mp. 226-228 °C; $[\alpha]_D$ +11.5° (c=1.0, methanol). Anal. ($C_{24}H_{36}N_2O$*2HCl) C, H, N.

[0109] The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine was prepared as follows:

22.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyano-ethenyl)phenyl]-3-phenylpropylamine

[0110] To a solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (13.87 g, 28.87 mmol) (prepared as described in WO 94/11337, Example 1) in DMF (140 mL) was added triethylamin (5.00 mL, 36.10 mmol), $Pd(OAc)_2$ (0.32 g, 1.44 mmol), tri(o-tolyl)phosphine (1.76 g, 5.77 mmol) and acrylonitrile (2.39 mL, 36.10 mmol). The reaction mixture was stirred overnight at 115 °C in a sealed flask equipped with a reflux condenser under nitrogen

atmosphere. The resulting mixture was concentrated, and the residue was dissolved in diethyl ether, washed with aqueous 2 M sodium hydroxide and water. The organic phase was dried ($MgSO_4$) whereafter petroleum ether was added to the organic phase and a precipitate was formed. Recrystallisation from ethanol yielded 5.50 g (42%). ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 6H), 0.95 (s, 6H), 2.15 (q, 2H), 2.35 (q, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.05 (s, 2H), 5.70 (d, 1H), 6.85 (d, 1H), 7.10-7.50 (m, 13H).

EXAMPLE 23

(R)-N,N-Diisopropyl-3-[5-3-(acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

[0111] To a solution of (R)-N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, (Example 22), (0.45 g, 1.23 mmol) in methanol (45 mL) was added acetic anhydride (0.23 mL, 2.47 mmol). The mixture was stirred for 3 h at room temperature and then evaporated to dryness. The residue was dissolved in H_2O, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried with $MgSO_4$, filtered and evaporated. The amine was dissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate formed was filtered off to give 0.55 g (100 %). ^{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

[0112] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropylamine (Example 22.1), (4.00 g, 8.84 mmol) was treated as described in Example 22, but the hydrogenation was performed at atmospheric pressure. Yield 1.35 g (38 %); ^{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-hydroxyphenyl]-3-phenylpropanamine hydrochloride.

[0113] A solution of (R)-N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine (Example 24), (2.00 g, 5.48 mmol), in conc. HCl was stirred at 50 °C for 2 h and then evaporated. The residue was dissolved in water, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was chromatographed on toluene-ethyl acetate-triethylamine-methanol, 7:2:1:1. The product was obtained from dietyl ether-hydrogen choride. Yield 0.9 g (39%); ^{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

[0114] To a solution of (R)-N,N-diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (obtained in Example 25), (0.50 g, 1.31 mmol) in ethanol (15 mL) and H_2O (10 mL) was added KOH (3.75 g, 66.8 mmol). The mixture was stirred overnight at 100 °C. The solvent was evaporated and the residue redissolved in H_2O and washed with diethyl ether. The aqueous layer was acidified with conc. HCl and the precipitate was collected by filtration and washed with 2 M HCl. The product was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using a gradient of 20-60% acetonitrile with 0.1% TFA. Fractions were pooled and hydrochloric acid (2 mL, conc.) was added and the solvent was evaporated. The residue was crystallised from methanol-diethyl ether to give 0.37 g (0.96 mmol, 74%); ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 4H), 2.76 (t, 2H), 3.04 (t, 2H), 3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.92 (d, 1H), 7.00 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 205-207 °C; $[\alpha]_D$ +3.7° (c=1.0, methanol). Anal. ($C_{24}H_{33}NO_3$*1.0HCl) C, H, N.

EXAMPLE 27

(R)-(N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine dihydrochloride

[0115] (R)-N,N-Diisopropyl-3- (5-azido-2-benzyloxyphenyl) -3-phenylpropanamine (0.90 g, 2.03 mmol) was dissolved in acetic acid and 10% Pd/C (210 mg, cat.) was added. The mixture was stirred and exposed to H_2 (1 atm.) at room temperature overnight. The Pd/C catalyst was filtered off, and the filtrate evaporated. The residue was dissolved in water and basified with aqueous 11 M sodium hydroxide, extracted with diethyl ether, dried ($MgSO_4$) filtrated and evaporated. The crude residue was chromatographed on silica (n-hexane-ethanol-triethylamine, 7:3:1). The hydrochloride was obtained from dietyl ether hydrogen chloride. The resulting oil was freeze-dried from water. Yield 0.30 g (37 %); ^{1}H NMR (DMSO) δ 1.13 - 1.33 (m, 12H), 2.47 (m, 2H), 2.82 (br, 1H), 2.98 (br, 1H), 3.57 (br, 2H), 4.38 (t, 1H), 6.96 (d, 1H), 7.08 (d, 1H), 7.19 (s, 1H), 7.22 (m, 1H), 7.32 (m, 4H), 10.05 (br, 2H), 10.13 (s, 1H); mp. 180-183 °C; $[\alpha]_D$ +21.0° (c=0.1, methanol). Anal. ($C_{21}H_{30}N_2O$*2.0HCl*0.5H_2O) C, H, N.

[0116] The starting compound (R)-N,N-diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

27.1 (R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine

[0117] To a mixture of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (10.00 g, 20.81 mmol) (prepared as described in WO 94/11337, Example 1) and Mg (1.57 g, 64.52 mmol) in THF (50 mL) was added 1,2-dibromoethane (3.59 mL, 41.63 mmol) and the solution was self-refluxing for a while. The mixture was refluxed for 1 h whereafter the solution was cooled and tosyl azide (4.10 g, 20.81 mmol) in diethyl ether (100 mL) was added with constant stirring while keeping the temperature at 0 °C wherafter the temperature was allowed to rise to room temperature for 4 h. A solution of tetra-sodium pyrophosphate decahydrate (4.46 g, 10.00 mmol) in 50 mL water was added. A precipitate was filtered off and the filtrate was evaporated. The residue was extracted with diethyl ether, the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (n-hexane-ethanol, 8:2). The product was crystallised from ethanol to give 1.15 g (13 %); IR (KBr) 2116 (N_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 12H), 2.10 (m, 2H), 2.33 (m, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.00 (s, 2H), 6.81 (d, 2H), 6.97 (s, 1H), 7.10 - 7.40 (m, 10H).

EXAMPLE 28

(R)-N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0118] To a solution of (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine (0.25 g, 0.76 mmol) in 0.78 M HCl (5.35 mL, 4.20 mmol) was added $NaNO_2$ (0.05 g, 0.76 mmol) dissolved in H_2O (0.4 mL) at -10 °C and the mixture was stirred for 20 minutes. To the mixture was added NaN_3, (57 mg, 0.88 mmol) dissolved in H_2O (0.4 mL), and the mixture was stirred at -10 °C for 30 minutes. The mixture was basified (pH 7-8) with aqueous 11 M sodium hydroxide and extracted with diethyl ether. The diethyl ether phase was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:2:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The precipitate was filtered to give (0.07 g, 0.18 mmol, 24%) of light-brown crystals. IR (KBr) 2111 (N_3) cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 2.50 (m, 2H), 3.04 (m, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.68 (s, 1H), 6.81 (m, 2H), 7.23 (m, 1H), 7.35 (m, 4H); mp. 131-134 °C; $[\alpha]_D$-5.0° (c=0.1, methanol).

[0119] The starting compound (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine was prepared as follows:

28.1 (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine

[0120] A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (7.30 g, 15.2 mmol) treated as described in Example 1.3 above. Yield 4.47 g (94 %).

28.2 (R)-N,N-Diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine

[0121] $NaNO_2$ (0.27 g, 4.30 mmol) was added to a mixture of hydrochloric acid (0.64 mL, 7.70 mmol, conc.) and p-methylaniline (0.41 g, 3.80 mmol) in ice-water (20 mL). The mixture was stirred at 0 °C for 10 min. and then added to an ice-cold solution of (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine (1.00 g, 3.21 mmol) in THF (3mL), H_2O (12 mL) and sodium hydroxide (0.69 g, 17.32 mmol). After stirring the mixture for 20 minutes, it was extracted with toluene, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on (toluene-ethyl acetate-triethylamine 8:1:1) to give 0.83 g, 1.93 mmol, (60%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 6H),

1.19 (d, 6H), 2.22 (m, 1H), 2.43 (m, 5H), 2.79 (m, 1H), 3.32 (m, 2H), 4.57 (d, 1H), 6.98 (d, 1H), 7.24 (m, 3H), 7.36 (m, 4H), 7.66 (m, 4H).

28.3 (R)-N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine

[0122] A solution of $Na_2S_2O_4$ (1.23 g, 12.8 mmol) in water (10 mL) was added to a solution of (R)-N,N-diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine (0.55 g, 1.28 mmol) in ethanol (50 mL) at 75 °C during 15 min. More dry $Na_2S_2O_4$ (1.23 g, 12.8 mmol) was added in 10 portions. Water was added to the solution which was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (n-hexane-ethanol-triethylamine 7:3:1) to give an oil. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. The solvent was evaporated, redissolved in water and vacuum-dried wich yielded 0.25 g (60%).

EXAMPLE 29

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine hydrochloride

[0123] A solution of (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (2.0 g, 4.86 mmol) in THF (50 mL) was added dropwise to LAH (0.28 g, 7.29 mmol). After stirring for 2 h, the reaction was quenched and the solvent evaporated. The residue was recrystallized from ethanol-water. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. White crystals were filtered off to give 0.82 g (46%); mp. 204-207 °C; $[\alpha]_D$ +12.8° (c=1.0, methanol); ^{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.

[0124] The starting compound (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine was prepared as follows:

29.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine

[0125] A solution of triethyl phosphonoacetate (6.93 mL, 34.92 mmol) in THF (50 mL) was added dropwise to NaH (0.84 g, 29.10 mmol, 80%). The mixture was cooled to 0 °C and (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine, prepared as described in Example 17.1, (5.00 g, 11.64 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 3 h at 0 °C. The solvent was evaporated and the residue was redissolved in toluene and washed twice with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 5.0 g (86%).

29.2 (R)-N,N-Diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine

[0126] (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine (3.0 g, 5.98 mmol) was treated as described in Example 1.3. Yield 2.0 g (81%); ^{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

[0127] (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (prepared in Example 7.1) (1.23 g, 3.62 mmol) was dissolved in methanol (20 mL). Ethylamine [3.62 mL, 21.7 mmol (6M hydrochloric acid in methanol)] and sodium cyanoborohydride (0.14 g, 2.17 mmol) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:3:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The resulting oil was stirred in diethyl ether over night to give crystals. Yield 0.70 g (44%); mp. 140-142 °C; $[\alpha]_D$ -5.0° (c=0.5, methanol); ^{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

[0128] A solution of N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (1.60 g, 3.44 mmol) was hydrogenated over Pd/C (160 mg, 10%) in acetic acid at room temperature overnight. The solution was basified with sodium hydroxide (11 M) and the mixture was filtered. The filtrate was extracted with ethyl acetate, dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluen-triethylamine 9:1). The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to give an oil. The oil was crystallised in 2-propanol to give 0.90 g (79%); mp. 153-155 °C; ^{1}H NMR (CD_3OD) δ 1.78 (m, 2H), 2.22 (m, 4H), 2.48 (m, 2H), 2.72 (s, 3H), 2.95 (br, 2H), 3.68 (m, 1H), 4.44 (t, 1H), 6.78 (t, 1H), 6.79 (d, 1H), 7.03 (t, 1H), 7.12 (d, 1H), 7.18 (t, 1H), 7.28 (t, 2H), 7.34 (d, 2H); Anal. ($C_{20}H_{25}NO$*1.0 HCl*0.3 2-propanol) C, H, N.

[0129] The starting compound N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

31.1 N-Cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0130] 5 M HCl-methanol (3.50 mL, 17.71 mmol) was added to a solution of cyclobutylamine (4.50 mL, 53.15 mmol) in methanol (14 mL). The mixture was added to 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (Example 20.1), (3.50 g, 8.86 mmol), followed by sodium cyanoborohydride (0.389 g, 6.20 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 92:4:4).Yield 2.61 g (65%); ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 5H), 2.14 (m, 4H), 2.47 (t, 2H), 3.16 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.47 (m, 12H).

31.2 N-Cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0131] 5 M HCl-methanol (0.46 mL, 2.32 mmol), formaldehyde (0.870 g, 28.97 mmol) and sodium cyanoborohydride (0.255 g, 4.056 mmol) were added to a solution of N-cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.61 g, 5.79 mmol) in methanol (8 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (hexane-triethylamine, 9:1). Yield 1.59 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.73 (m, 2H), 1.91 (m, 2H), 2.06 (s, 3H), 2.16 (m, 4H), 2.68 (m, 1H), 4.38 (t, 1H), 5.00 (s, 2H), 6.72 (d, 1H), 7.12-7.58 (m, 12H).

EXAMPLE 32

N-Cyclopentyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

[0132] N-Cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.46 g, 5.14 mmol) was treated as described in Example 31. The crude was not chromatographed but crystallised from aqueous ethanol. Yield 1.24 g (70%) ^{1}H NMR (DMSO) δ 1.48 (br, 1H), 1.66 (br, 2H), 1.85 (br, 1H), 2.46 (br, 2H), 2.68 (s, 3H), 2.87 (br, 2H), 3.53 (m, 1H), 4.35 (t, 1H), 6.77 (t, 1H), 6.83 (d, 1H), 7.01 (t, 1H), 7.16 (t, 1H), 7.27 (t, 3H), 7.33 (d, 2H), 9.57 (br, 1H), 10.85 (br, 1H); mp 169-172 °C; Anal. ($C_{21}H_{27}NO$*HCl) C, H, N.

[0133] The starting compound N-cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

32.1 N-Cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0134] 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal, prepared as described in Example 20.1, (7.00 g, 17.71 mmol) was treated with cyclopentylamine as described in Example 31.1. Yield 4.9 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 2H), 1.40-1.80 (m, 6H), 2.18 (m, 2H), 2.55 (t, 2H), 2.98 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.45 (m, 12H).

32.2 N-Cyclopenthyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

[0135] A solution of N-cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (3.50 g, 7.53 mmol) was treated as described in Example 31.2. Yield 2.46 g (68%); ^{1}H NMR ($CDCl_3$) δ 1.10-1.80 (m, 8H), 2.19 (m, 5H), 2.36 (m, 2H), 2.58 (m, 1H), 4.37 (t, 1H), 4.98 (s, 2H), 6.72 (d, 1H), 7.10-7.50 (m, 12H).

EXAMPLE 33

N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropanaminehydrochloride

[0136] LAH (0.94 g, 24.8 mmol) was added to a solution of N,N-diisopropyl-3-(2-aminophenyl) -3-phenylpropenylamide (1.6 g, 4.98 mmol) in THF (90 mL). The mixture was stirred for 72 h at room temperature. The reaction was quenched and the solvent evaporated. The crude residue was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using 20 % acetonitrile with 0.1% TFA. Hydrochloric acid was added to the pure fractions and the solvent was evaporated. The residue was redissolved in water and freeze-dried giving 88 mg (5%) ; mp 138 - 142 °C; ^{1}H NMR (DMSO) δ 1.25 (m, 12H), 2.47 (m, 1H), 2.65 (m, 1H), 2.87 (m, 1H), 3.13, (m, 1H), 3.59 (br, 2H), 4.58 (t, 1H), 7.20 - 7.37 (m, 5H), 7.42 (m, 2H), 7.54 (d, 2H), 9.94 (br, 2H). Anal. ($C_{21}H_{30}N_2$*HCl*H_2O) C, N, H: calcd.8.5; found 7.9.

[0137] The starting compound N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide was prepared as follows:

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

[0138] A slurry of ice (500 mL), hydrochloric acid (16.8 mL, 202 mmol, conc.), 2-aminobenzophenone (20.00 g, 101 mmol) and $NaNO_2$ (9.0 g, 131 mmol) were added to a stirred solution of 2,6-dimethylphenol (18.40 g, 151 mmol) and sodium hydroxide (16.20 g, 404 mmol) in ice-cold water (100 mL). After 20 minutes the mixture was extracted with diethyl ether. The organic phase was washed with hydrochloric acid (6 M), $NaHCO_{3(aq)}$, dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene) and pure fractions were pooled and evaporated to give a red oil. The oil was crystallised in hexane/toluene to give 7.73 g (23%).

33.2 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone

[0139] A mixture of 2-(3,5-dimethyl-4-hydroxyphenylazo)-benzophenone (7.73 g, 23.41 mmol) and tosyl chloride (9.4 g, 49 mmol) in pyridine (20 mL) was stirred at 90 °C for 9 h. Water was added and the mixture was extracted with diethyl ether. The organic phase was washed with sodium hydroxide (2 M) and hydrochloric acid (2 M), dried ($MgSO_4$) and the solvent evaporated. The product was crystallised in ethanol to give 7.62 g (67%); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 6H), 2.49 (s, 3H), 7.05 (s, 2H), 7.37 (m, 4H), 7.48 (m, 1H), 7.62 (m, 3H), 7.82 (m, 5H).

33.3 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenylazo)phenyl]-3-phenylpropenamide

[0140] 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone (7.22 g, 14.9 mmol) was treated as described in Example 4.2 but with 3 eq of N,N-diisopropylacetamide diethylphosphonate and sodium hydride. Yield 4.5 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H), 0.82 (br, 3H), 1.28 (d, 3H), 1.42 (d, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.45 (s, 3H), 3.25 (m, 1H), 4.28 (m, 1H), 6.05 and 6.63 (s, 1H), 7.00 - 7.90 (m, 15H).

33.4 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenylazo)phenyl]-3-phenylpropenamide

[0141] A solution of potassium hydroxide (10.3 mL, 6 M) and N,N-diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenylazo)phenyl]-3-phenylpropenamide (3.5 g, 5.74 mmol) in ethanol (110 mL) was refluxed for 1 h. The mixture was acidified with hydrochloric acid (conc.) and the solvent evaporated. The residue was partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene-ethyl acetate 9:2). Yield 1.3 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.71 (d, 3H), 0.80 (br, 3H), 1.27 (d, 3H), 1.40 (d, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.25 (m, 1H), 4.35 (m, 1H), 5.52 (brd, 1H), 6.05 and 6.60 (s, 1H), 7.00 - 7.80 (m, 11H).

33.5 N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropenamide

[0142] N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenylazo)phenyl]-3-phenylpropenamide (2.58 g, 5.68 mmol) was treated as described in Example 28.3. The crude residue gave crystals from aqueous ethanol. Yield 1.23g (67%).

EXAMPLE 34

N,N-Diisopropyl-3-(benzoxazol-2-yl)-3-phenylpropanamine,hydrochloride

[0143] A mixture of N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (2.51 g, 8.6 mmol), 75% aqueous ethanol (15 mL) and 2 M NaOH (8.5 mL, 17 mmol) was refluxed over night. After evaporation of the solvent, the residue

was made acidic with 2 M HCl and the solvent was evaporated. A mixture of the residual semicrystalline oil was heated with o-aminophenol (1.8 g, 16.5 mmol) and polyphosphoric acid (12 g) at 200°C for 2 hours under N_2. The somewhat cooled hard solid was dissolved in water and washed once with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether/triethylamine 97:3). The pure amine was precipitated as hydrochloride from diethyl ether affording white crystals, 1.27 g (39%): mp 197-198°C; ^1H NMR ($CDCl_3$) δ 1.49 (m, 12H), 2.80-3.20 (m, 4H), 3.48 (br, 2H), 4.45 (t, 1H), 7.25-7.48 (m, 8H), 7.70 (m, 1H), 11.48 (br, 1H).

[0144] The starting compound N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine was prepared as follows:

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

[0145] Sodium hydride, 80% in mineral oil (2.82 g, 94 mmol), was washed with petroleum ether and dried under a N_2-stream. Dry DMF (100 mL) was added. Benzyl cyanide (12.1 g, 103 mmol) was added to the stirred suspension over a period of 20 min. The temperature rose to approx. 45°C. The mixture was stirred for another 15 min. 2-Chloroethyldiisopropylamine (15.4 g, 94 mmol) was added. All the amine was consumed within 30 min. Most of the DMF was evaporated under reduced pressure and the residue was dissolved in water/diethyl ether. The aqueous phase was extracted once with diethyl ether and the combined organic phases were extracted twice with 2 M HCl. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent was evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 40:1), affording the title compound, 16.8 g (67%), as a colourless liquid. ^1H NMR ($CDCl_3$) δ 1.01 (m, 12H), 1.97 (m, 2H), 2.62 (m, 2H), 3.00 (m, 2H), 4.02 (dd, 1H), 7.17-7.40 (m, 5H).

34.2 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamine

[0146] N,N-Diisopropyl-3-cyano-3-phenylpropanamine (11.6 g, 47.5 mmol) was mixed with H_2SO_4 (90%, 100 mL) and the mixture was stirred at 100°C for 30 min. The reaction mixture was poured on ice, made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated, affording the title compound as a colourless oil, 12.4 g (100%); ^1H NMR ($CDCl_3$) δ 1.26 (m, 12H), 2.14 (m, 1H), 2.60 (m, 1H), 2.73 (t, 2H), 3.31 (m, 2H), 3.86 (t, 1H), 6.06 (br, 2H), 7.51- 7.61 (m, 5H).

34.3 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine

[0147] N,N-Diisopropyl-3-carbamyl-3-phenylpropanamine (26.5 g 0.100 mol) was added into aqueous ethanol (90%, 300 mL) containing conc. HNO_3 (13.3 g, 0.21 mol) and refluxed for five days. Most of the solvent was evaporated under reduced pressure and the residue was mixed with water/diethyl ether. The organic phase was washed once with water. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 97/3), to afford the title compound as a colourless liquid, 20.1 g (68.7%): ^1H NMR ($CDCl_3$) δ 0.96 (m, 12H), 1.21 (t, 3H), 1.81 (m, 1H), 2.22 (m, 1H), 2.40 (t, 2H), 3.66 (dd, 1H), 4.12 (m, 2H), 7.20-7.32 (m, 5H).

EXAMPLE 35

N,N-Diisopropyl-3-(oxazol-5-yl)-3-phenylpropanaminehydrochloride

[0148] Freshly distilled methylisonitrile (1.66 g, 40.4 mmol) was dissolved in dry THF (75 mL) under N_2-atmosphere and the mixture was cooled to -78°C. 1.4 M n-BuLi (29 mL, 40.5 mmol) was slowly added to the solution, followed by N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (4.71 g, 16.2 mmol) in THF (10 mL). The reaction temperature was allowed to rise to -20°C, at which the reaction was quenched with HOAc (10 mL). The solvent was evaporated and the residue was mixed with diethyl ether/water. The organic phase was washed once with water and the combined aqueous phases were made alkaline with 11 M NaOH and extracted twice with diethyl ether. The organic phases were put together, dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 490:10:1). The pure amine was precipitated with HCl-saturated diethyl ether, affording the title compound as a glassy oil, 1.4 g (48%). ^1H NMR (CD_3OD) δ 1.21-1.40 (m, 12H), 2.57 (m, 1H), 2.68 (m, 1H), 2.91 (m, 1H), 3.23 (m, 1H), 3.72 (m, 2H), 4.41 (dd, 1H), 7.39 (m, 5H), 7.52 (s, 1H), 9.13 (s, 1H).

EXAMPLE 36

N,N-Diisopropyl-3-(imidazol-4(5)-yl)-3-phenylpropanamine dihydrochloride

[0149] N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was mixed with formamide (5 mL). The mixture was heated at 175°C for 6 hours. The solvent was evaporated under vacuum (1 mm Hg) and the residue was partitioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The light brown oil was dissolved in diethyl ether and added to a suspension of lithium aluminium hydride (LAH) (0.70 g, 5.4 mmol) in diethyl ether. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched, and the solvent was evaporated. The crude amine was dissolved in EtOAc and precipitated as a hydrochloride salt with HCl-saturated diethyl ether to afford the title compound as hygroscopic crystals, 0.32 g (35%) : ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 12H), 2.80 (m, 2H), 3.00 (m, 1H), 3.16 (m, 1H), 3.64 (br, 2H), 4.41 (m, 1H), 6.89 (s, 1H), 7.27-7.41 (m, 5H), 8.78 (s, 1H), 10.32 (br, 2H).

[0150] The starting compound N,N-diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was prepared as follows:

36.1 3-Cyano-3-phenylpropanoic acid

[0151] Ethyl cinnamate (85.3 g, 0.484 mol), potassium cyanide (64.2 g, 0.986 mol) and ammonium chloride (38.9 g, 0.726 mol) were mixed with aqueous DMF (90%, 360 mL). The mixture was stirred at 105°C for 7 hours. The somewhat cooled mixture was filtered and most of the DMF was evaporated. The residue was taken up in diethyl ether and 1 M HCl. The aqueous phase was extracted twice with diethyl ether. The combined diethyl ether phases were evaporated and the black oil was suspended in EtOH (200 mL) and 2 M NaOH (250 mL) and stirred at ambient temperature for 2 hours. The mixture was diluted with brine (200 mL) and water (400 mL) and washed twice with diethyl ether. After acidification (12 M HCl) the aqueous phase was extracted three times with diethyl ether. The pooled organic phases were dried (Na_2SO_4) and the solvent evaporated affording the title compound as a black oil, 74 g (87%): ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.17 (d, 3H), 1.22 (d, 6H), 2.68 (dd, 1H), 3.16 (dd, 1H), 3.4 (br, 1H), 3.76 (m, 1H) 4.19 (dd, 1H), 7.31 (m, 5H), 8.9 (br, 1H).

36.2 N,N-Diisopropyl-3-cyano-3-phenylpropanamide

[0152] 3-Cyano-3-phenylpropanoic acid (67.7 g, 0.389 mol) was dissolved in 2-PrOH. To the filtered acid solution was carefully added KOH (18.4 g, 0.33 mol) dissolved in 2-PrOH (200 mL), diethyl ether (100 mL) was added and the precipitate was filtered off. The dried acid salt (51.9 g, 0.24 mol) was suspended in benzene (400 mL) and oxalyl chloride was carefully added. The reaction mixture was stirred at 80°C for 2 hours. The solvent was evaporated and the residue was co-evaporated twice with benzene. The brown oil was dissolved in benzene (200 mL) and cooled in an icebath. A solution of diisopropylamine (82 g, 0.81 mol) in benzene (200 mL) was added to the stirred reaction mixture during 45 min. The mixture was left to slowly warm up to room temperature overnight. The solvent was evaporated and the residue was taken up in diethyl ether and 1 M HCl. The organic phase was washed once with water, once with 1 M NaOH, again with water, dried (Na_2SO_4) and the solvent evaporated to afford the title compound as a dark brown oil, 41.7 g (41%): ^{1}H NNR ($CDCl_3$) δ 1.07 (d, 3H), 1.17 (d, 3H), 1.36 (m, 6H), 2.77 (m, 1H), 2.97 (m, 1H), 3,51 (br, 1H), 3.81 (m, 1H), 4.50 (dd, 1H), 7.39 (m, 5H).

36.3 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide

[0153] N,N-Diisopropyl-3-cyano-3-phenylpropanamide (21.1 g, 82 mmol) was dissolved in EtOH (130 mL) and 2 M NaOH (100 mL). Hydrogen peroxide (30%, 20.2 mL, 200 mmol) was added and the mixture was stirred at ambient temperature for two hours. The resulting precipitate was filtered, washed with water and dried, yielding the title compound as white crystals, 15.6 g (69%): ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.19 (d, 3H), 1.31 (m, 6H), 2.51 (dd, 1H), 3.30 (dd, 1H), 3.41 (m, 1H), 4.02 (m, 1H), 4.18 (dd, 1H), 5.7 (br, 1H), 6.4 (br, 1H), 7.21-7.42 (m, 5H).

36.4 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide

[0154] N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide was treated as described in Example 34:3 (two days of reflux and no chromatography) which gave the title compound as a colourless semicrystalline oil, 15.9 g (93%): ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 9H), 1.36 (m, 6H), 2.53 (dd, 1H), 3.18 (dd, 1H), 3.4 (br, 1H), 3.98 (m, 1H), 4.15 (m, 3H), 7.31 (m, 5H).

36.5 N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide

[0155] The method described for Example 35 above was used, starting from N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide. The crude was chromatographed on silica (petroleum ether-EtOAc, 3:2), affording the title compound as a light yellow oil, 0.77 g (46%): ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H), 1.14 (d, 3H), 1.29 (m, 6H), 2.98 (m, 2H), 3.4 (br, 1H), 3,93 (m, 1H), 4.79 (t, 1H), 6.82 (s, 1H), 7.28 (m, 5H), 7.76 (s, 1H).

EXAMPLE 37

N,N-Diisopropyl-3-(oxazol-2-yl)-3-phenylpropanamine hydrochloride

[0156] A mixture of N,N-diisopropyl-3-carbamoyl-3-phenylpropanamine, prepared in Example 34.2 (4.05 g, 15.4 mmol), 1,2-dichloroethyl ethyl ether (2,32 g, 16.2 mmol), water (0.300 g, 16.6 mmol) and formic acid (50 mL) was stirred at 75°C for 3 hours. The formic acid was evaporated and the residue was dissolved in water/diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine 97:3). The pure amine was precipitated as hydrochloride salt with HCl-saturated diethyl ether, affording the title compound as white crystals, 0.61 g (12%): mp 157-158°C; ^{1}H NMR (DMSO(d_6)) δ 1.11 (m, 12H), 2.35 (m, 1H), 2.63 (m, 1H), 3.03 (m, 2H), 3.56 (m, 2H), 4.45 (m, 1H), 7.21-7.40 (m, 6H) 8.06 (d, 1H), 10.20 (br, 1H).

EXAMPLE 38

N,N-Diisopropyl-3-phenyl-3-(thiazol-2-yl)propanamine hydrochloride

[0157] The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine (1.11 g, 4.0 mmol) yielded white crystals of the title compound, 1.12 g (82%): mp 155-156°C; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 12H), 2.75-3.15 (m, 4H), 3.60 (m, 2H), 4.45 (t, 1H), 7.25-7.36 (m, 6H), 7.71 (d, 1H), 11.30 (br, 1H).

[0158] The starting compound N,N-diisopropyl-3-phenyl-3-thiocarbamoylpropanamine was prepared as follows:

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

[0159] H_2S was bubbled into a solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine, prepared in Example 34.1, (3.45 g, 14.3 mmol) and triethylamine (2.0 g, 20 mmol) in dry pyridine (10 mL) until saturation was achieved. The stirred reaction was held under H_2S-atmosphere at 65°C for 5 days. The pyridine was evaporated and the crude product was chromatographed on silica (chloroform-methanol-conc. ammonia 380:20:1), yielding the title compound as a colourless glassy oil, 3.1 g (78%): ^{1}H NMR ($CDCl_3$) δ 0.99 (m, 12H), 2.07 (m, 1H), 2.40 (m, 3H), 3.05 (m, 2H), 4.10 (t, 1H), 7.20-7.45 (m 5H), 7.7-8.1 (b, 1H), 8.0-8.5 (br, 1H).

EXAMPLE 39

N,N-Diisopropyl-3-(4-methylthiazol-2-yl)-3-phenylpropanamine hydrochloride

[0160] The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine, prepared in Example 38.1, (1.5 g, 5,4 mmol), and 2-chloroacetone (0.75 g, 8.1 mmol) yielded the title compound as a white amorphous substance, 1.1 g (56%): mp 178-181°C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 12H), 2.50 (s, 3H), 2.98 (m, 3H), 3.18 (m, 1H), 3.60 (m, 2H), 6.94 (d, 1H), 7.30-7.47 (m, 5H), 11.15 (br, 1H).

EXAMPLE 40

N,N-Diisopropyl-3-(thiazol-5-yl)-3-phenylpropanamine hydrochloride

[0161] The title compound was prepared in an analogous manner to that described in Example 35. Reaction with N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine (1.14 g, 3.7 mmol) gave a crude that was chromatographed on silica (petroleum ether-triethylamine 97:3), affording white crystals of the title compound, 0.19 g (30%): mp 193-194°C; ^{1}H NMR ($CDCl_3$) δ 1.1.34 (m, 12H), 2.85 (m, 4H), 5.56 (m, 2H), 4.29 (t, 1H), 7.26-7.39 (m, 5H), 7.73 (s, 1H), 8.71 (s, 1H) 11.61 (br, 1H).

[0162] The starting compound N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine was prepared as

follows:

40.1 N,N-Diisopropyl-3-ethoxythiocarbonyl-3-phenylpropanamine

[0163] HCl-gas was bubbled through an ice-cold solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine (2.9 g, 12 mmol), prepared in Example 34.1, in dried ethanol (50 mL, molecular sieve 3 Å) until saturation. The stirred reaction was held under HCl-atmosphere at room temperature overnight. The solvent was carefully evaporated and the remaining oil was dissolved in dry pyridine (100 mL). To this solution was added triethylamine (5.7 g, 56 mmol) and to the now thick suspension was bubbled H_2S until saturation was achieved. The dark olive-green reaction mixture was held under a H_2S-atmosphere at 65°C overnight. The solvent was evaporated and the residue was partioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 198:1:1), affording the title compound as a straw-coloured liquid, 1.24 g (33%): ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 12H), 1.34 (t, 2H), 1.97 (m, 1H), 2.37 (m, 3H), 2.98 (m, 2H), 4.10 (t, 1H) 4.46 (m, 2H), 7.13-7.39 (m, 5H).

EXAMPLE 41

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl) - propanamine fumarate

[0164] To a suspension of lithium aluminium hydride (LAH) (0.51 g 13.3 mmol) in THF (30 mL), N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide (2.0 g, 5.33 mmol) was added and warmed to 50°C overnight. The reaction mixture was quenched and the solvent was evaporated. The residue was dissolved in diethyl ether and extracted twice with 2 M HCl, and the combined aqueous phases were washed twice with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted three times with diethyl ether, the combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent evaporated. The pure amine was crystallised from methanol as its fumarate, yielding the title compound as white crystals, 1.52 g (58%): mp 203-205°C; ^{1}H NMR (DMSO) δ 1.00 (d, 12H), 2.02 (q, 2H), 2.33 (m, 2H), 3.18 (m 2H), 4,62 (t, 1H), 6.50 (s, 1H), 6.68-7.18 (m, 6H), 7.28 (t, 1H).

[0165] The starting compound N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide was prepared as follows:

41.1 N,N-Diisopropyl-3-(2-thienyl)propenamide

[0166] 2-Bromothiophene (2.28 g, 14.0 mmol), N,N-diisopropylacrylamide (1.55 g, 10.0 mmol), palladium(II)acetate (34 mg, 0.15 mmol), tri-o-tolylphosphine (183 mg, 0.6 mmol), tri-n-butyl amine (2.04 g, 11.0 mmol) and dry DMF (5 mL) were mixed under a N_2-atmosphere. The mixture was heated to 130°C for 9 hours. Diethyl ether and H_2O was added to the somewhat cooled mixture. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed twice with 2 M HCl, once with water, once with brine, and dried ($MgSO_4$), and the solvent was then evaporated. The crude product was chromatographed on silica (petroleum ether-ethyl acetate 4:1), affording a yellow oil, 1.58 g (66%): ^{1}H NMR ($CDCl_3$) δ 1.35 (br, 12H), 3.9 (br, 1H), 4.1 (br 1H), 6.65 (d, 1H), 7.00-7.30 (m, 3H), 7.72 (d, 1H).

41.2 2-Methoxyphenyllithium

[0167] 2-Methoxybromobenzene (8.44 g 45.1 mmol) was dissolved in dry diethyl ether (15 mL). The mixture was cooled to -78°C. n-BuLi (17.8 mL, 45.0 mmol) was added and the mixture was stirred for one hour at -78°C and then for 20 min. at -10°C. The aryl lithium solution was used immediately.

41.3 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide

[0168] Copper(I)bromide dimethyl sulfide complex (4.63 g 22.5 mmol) was dissolved in dimethyl sulfide (18 mL), and diethyl ether (15 mL). The solution was cooled to 0°C, whereafter 2-methoxyphenyllithium (41.2) (45 mmol) was added. After 10 min., the temperature was lowered to -78°C. Trimethylsilylchloride (4.89 g, 45.0 mmol) was added, followed by N,N-diisopropyl-3-(2-thienyl)propenamide (41.1) (3.56 g, 15 mmol) in diethyl ether (20 mL). The temperature was allowed to slowly rise to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and conc. ammonia (10 mL). Diethyl ether (80 mL) was added and the mixture was filtered through Celite. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed once with brine and dried ($MgSO_4$). The solvent was evaporated and the crude product was chromatographed on silica (petroleum ether-ethyl

acetate 3:1), affording a yellow oil, 3.75 g (73%): ^{1}H NMR ($CDCl_3$) d 1.12 (t, 6H), 1.29 (t, 6H), 3.02 (m, 2H), 3.4 (br, 1H), 3.80 (s, 3H), 4.03 (m, 1H), 5.26 (t, 1H), 6.8-7.3 (m, 7H).

41.4 N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide

[0169] A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide (2.37 g, 6.9 mmol) in dichloromethane(35 mL) was cooled down to -78°C and boron tribromide (5.9 g 23.57 mmol) was added. The reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched by slow addition of water (20 mL). The pH was adjusted to around 6 with $NaHCO_3$(s) and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent was evaporated. This crude product (2.46 g, 107%) was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.20 (m, 6H), 1.35 (d, 3H), 3.16 (m, 2H), 3.4 (br, 1H), 4.0 (m, 1H), 5.24 (dd. 1H), 6.7-7.2 (m, 7H).

[0170] Examples 42-54 and 57 and 58 were prepared with the methodology described for Example 41, starting with the appropriate acrylamides and aryl bromides.

EXAMPLE 42

N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-(2-thienyl)propanamine

[0171] The crude product was crystallised from petroleum ether/ethyl acetate affording the title compound, 0.41 g as slightly pink crystals: mp 102-109°C; ^{1}H NMR ($CDCl_3$) δ 1.11 (m, 12H), 2.01 (m, 1H), 2.41 (m, 2H), 2.72 (m, 1H), 3.26 (m, 2H), 4.66 (dd, 1H), 6.30 (dd, 1H), 6.45 (d, 1H), 6.73 (d, 1H), 6.91-7.00 (m, 2H), 7.17 (dd, 1H).

EXAMPLE 43

N,N-Diisopropylamine-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine, fumarate

[0172] White crystals, 0.95 g: mp 153-155°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 2H), 3.05 (m, 2H), 3.68 (m, 2H), 3.85 (s, 3H), 4.71 (t, 1H), 6.68 (s, 2H), 6.89-7.03 (m, 4H), 7.20-7.30 (m, 3H).

EXAMPLE 44

N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-(2-thienyl)propanamine fumarate

[0173] White crystals, 1.52 g: mp 103-109°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.46 (m, 2H), 3.04 (m, 2H), 3.66 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.60 (t, 1H), 6.46-6.58 (m, 2H), 6.68 (s, 2H), 6.91-6.97 (m, 2H), 7.09- 7.26 (m, 2H).

EXAMPLE 45

N,N-Diisopropyl-3-(3-methoxyphenyl)-3-(2-thienyl)propanamine hydrochloride

[0174] White crystals, 1.16 g: mp 95-97°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.49 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.68 (m, 2H), 3.77 (s, 3H), 4.31 (t, 1H), 6.83 (m, 1H), 6.68-7.02 (m, 4H), 7.27 (m, 2H).

EXAMPLE 46

N,N-Diisopropyl-3-(4-methoxyphenyl)-3-(2-thienyl) - propanamine hydrochloride

[0175] White amorphous substance, 0.50 g: mp 157-160°C; ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.47 (m, 2H), 2.94 (m, 1H), 3.12 (m, 1H) 3.68 (br, 2H), 3.77 (s, 3H), 4.28 (t, 1H), 6.87-7.00 (m, 4H), 7.23-7.32 (m, 3H).

EXAMPLE 47

N-Isopropyl-N-methyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine fumarate

[0176] White crystals, 1.32 g: mp 141-143°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.50 (m, 2H), 2.73 (s, 3H), 3.04 (m, 2H), 3.58 (m, 1H), 3.84 (s, 3H), 4.73 (t, 1H), 6.68 (s, 2H), 6.96 (m, 4H), 7.24 (m, 3H).

EXAMPLE 48

N,N-Diisopropyl-3-phenyl-3-(2-thienyl)propanamine, hydrochloride

[0177] White crystals, 0.74 g: mp 165-166°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.52 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.70 (br, 2H), 4.34 (t, 2H), 6.92-7.04 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 49

N-Cyclohexyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

[0178] White crystals, 1.1 g: mp 197-199°C; ^{1}H NMR (CD_3OD) δ 1.15-1.52 (br, 5H), 1.68 (br, 1H), 1.90 (br, 4H), 2.51 (br, 2H), 2.78 (s, 3H), 2.91-3.40 (m, 3H), 4.31 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 50

N,N-Diethyl-3-phenyl-3-(2-thienyl)propanamine fumarate

[0179] White crystals, 1.7 g (tot. 49 %): mp 135-137°C; ^{1}H NMR (CD_3OD) δ 1.22 (t, 3H), 2.50 (m, 2H), 2.90-3.26 (m, 6H), 4.30 (t, 1H), 6.68 (s, 2H), 6.92-7.03 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 51

N-Isopropyl-N-methyl-3-phenyl-3-(2-thienyl)propanaminehydrochloride

[0180] White crystals, 1.6 g: mp 139-144°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.52 (m, 2H), 2.75 (s, 3H), 3.03 (m, 2H), 3.59 (m, 1H), 4.32 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 52

N-[3-Phenyl-3-(2-thienyl)propyl]pyrrolidine fumarate

[0181] Crystallisation from 2-propanol, 1.1 g: mp 144-145°C; ^{1}H NMR (CD_3OD) δ 2.02 (m, 4H) 2.31 (m, 2H), 2.97-3.42 (m, 6H), 4.29 (t, 1H), 6.69 (s, 2H), 6.91-7.01 (m, 2H), 7.18-7.38 (m, 6H).

EXAMPLE 53

N-[3-Phenyl-3-(2-thienyl)propyl]piperidine hydrochloride

[0182] The hydrochloride was crystallised from ethylmethylketone, 0.84 g: mp 193-194°C; ^{1}H NMR (CD_3OD) δ 1.40-2.00 (b, 6H), 2.54 (m, 2H), 2.82-3.80 (m, 6H), 4.29 (t, 1H), 6.91-7.03 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 54

N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine hydrochloride

[0183] White crystals, 2.1 g: mp 205-210°C; ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 12H), 2.18 (s, 3H), 2.63 (m, 2H), 2.95 (m, 2H), 3.54 (m, 4H), 4.61 (t, 1H), 6.76-7.01 (m, 5H), 7.16 (d, 1H).

EXAMPLE 55

(R*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

[0184] To the racemic free base of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-2-thienylpropanamine (20 g, 0.06 mol), prepared in Example 54, in abs. ethanol (50 g) was added L-(+)-tartaric acid (9.5 g 0.063 mol) in ethanol (60 g). The salt formed was filtered off and crystallised twice from ethanol/methanol 10/1, 10 mL per gram of crystals, affording the title compound as white crystals, (6.8 g, 14.1 mmol): mp 214-215°C; $[\alpha]_{Hg}$=+17.3° (c=3.82 in methanol).

EXAMPLE 56

(S*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

[0185] From the mother liquid from the first crystallisation to obtain (R*) N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine in Example 55, the free base was recovered. The amine was treated with a 5% excess of D-(-)-tartaric acid in ethanol as above, yielding the title compound as white crystals, 6.1 g (12.7 mmol): mp 214°C; $[\alpha]_{Hg}$=-17.5° (c=3.85 in methanol).

EXAMPLE 57

N,N-Diisopropyl-3-phenyl-3-(3-thienyl)propanamine hydrochloride

[0186] White crystals, 0.94 g: mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 12H), 2.87 (m, 4H), 3.56 (br, 2H), 3.98 (t, 1H), 6.94 (dd, 1H), 7.27 (m, 7H), 11.4 (br, 1H).

[0187] The starting compound was prepared as follows:

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

[0188] Sodium hydride, 60% in mineral oil (3.9 g, 98 mmol), was washed several times with petroleum ether and dried under a stream of nitrogen. Sodium-dried THF was added followed by diethyl N,N-diisopropyl acetamidephosphonate (27.4 g, 98 mmol). When the evolution of gas had ceased, thiophene-3-aldehyde (10.0 g, 89.2 mmol) in THF (50 mL) was added at such a rate that the temperature never exceeded 45°C. After one hour of stirring at ambient temperature, the reaction was quenched with 4 mL of water and stirred for another hour. The solvent was evaporated and the residue was taken up in diethyl ether/2M NaOH. The organic phase was washed once with water and once with brine, dried (Na_2SO_4) and evaporated. The crude was chromatographed on silica (petroleum ether-ethyl acetate 4:1) affording the title compound as a light-brown oil, 14.8 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.37 (b, 12H), 3.86 (br, 1H), 4.10 (br, 1H), 6.68 (d, 1H), 7.27-7.41 (m, 3H), 7.59 (d, 1H).

EXAMPLE 58

N,N-Diisopropyl-3-(2-furanyl)-3-phenylpropanamine hydrochloride

[0189] White crystals, 60 mg: mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (br, 12H), 2.64 (m, 1H), 2.85 (m, 3H), 3.55 (m, 2H), 3.98 (t, 1H), 6.16 (d, 1H), 6.31 (dd, 1H), 7.30 (m, 6H), 11.4 (br, 1H).

[0190] The starting compound was prepared as follows:

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

[0191] The title compound was obtained from furfural with the procedure described in Example 57.1, as a colourless oil, 11.2 g (75%): ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 12H), 4.0 (br, 2H), 6.41 (m, 2H), 6.76 (d, 1H), 7.38 (m, 2H).

EXAMPLE 59

N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl - propanamine fumarate

[0192] A solution of N,N-diisopropyl-3-(N-methyl-pyrr-2-yl)-3-phenyl-propanamide (4.92 g, 15.7 mmol) in THF (75 mL), was dropped into a stirred mixture of LAH (2.38 g, 62.8 mmol). Stirring was continued at 50 °C overnight. Standard work-up gave the amine as a yellow oil, which was isolated as the fumarate salt, 2.74 g (42 %): m.p. 134-6°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 6H), 1.29 (d, 6H), 2.24 (m, 1H), 2.48 (m, 1H), 2.97 (dt, 1H), 3.26 (dt, 1H), 3,32 (s, 3H), 3.69 (septet, 2H), 4.08 (t, 1H), 6.05 (t, 1H), 6.16 (m, 1H), 6.57 (dd, 1H), 6.71 (s, 2H) and 7.19-7.34 (m, 5H).

[0193] The starting compound was prepared as follows:

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

[0194] The title compound was prepared from N-methyl-2-pyrrolaldehyde and N,N-diisopropyl-dimethylphosphon acetamide analogously to Example 4.2, giving 7.61 g (92%): ^{1}H NMR($CDCl_3$) δ 1.32 (d, 6H), 1.35 (d, 6H), 3.68 (s, 3H), 4.00 (m, 2H), 6.13 (t, 1H), 6.55-6.66 (3H) and 7,57 (d, 1H).

59.2 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl - propanamide

[0195] The title compound was prepared from N,N-diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide by a method analogous to that described in Example 41.3, giving 4.92 g (78 %): ^{1}H NMR ($CDCl_3$) δ 0.85-1.32 (4d from rotamers, 12H), 2.91 (d, 2H), 3.31 (s, 3H) 3.45 (m, 1H), 3.88 (m, 1H), 4.65 (t, 1H), 6.07 (2H), 6.50 (dd, 1H) and 7.15-7.22 (5H).

EXAMPLE 60

3-(N-Methylpyrrol-2-yl)-3-phenyl-1-pyrrolidinopropane fumarate

[0196] The title compound was prepared analogously to Example 59, using N,N-tetramethylene-dimethylphosphon acetamide, yield 950 mg (36 % tot.): m.p. 194-5°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 12H), 2.2-2.6 (m, 2H) 3.05 (m, 2H), 3.66 (sept., 2H), 4.03 (t, 1H), 6.02 (two d, 2H), 6.64 (t, 1H), 6.69 (s, 2H) and 7.28 (m, 5H).

BIOLOGICAL EVALUATION

[0197] The pharmacological activity of compounds prepared in the Examples was tested using in vitro methods.

Functional in vitro studies

[0198] Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilise for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilisation period.

[0199] Carbachol (carbamylcholine chloride) was used as the standard muscarinic receptor agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by two consecutive additions of a submaximal concentration (3 x 10^{-6} M) of carbachol. A concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}- values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1) (Schild, H.I., Br. J. Pharmacol. Chemother. 1949, 4, 277-280), where [A] is the concentration of test compound:

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

[0200] The KB values obtained are presented in Table 1 below.

Table 1

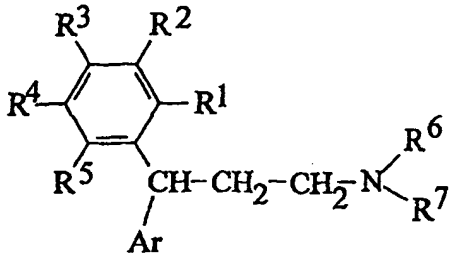
Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
1	499	23	1.05	45	51
3	236	24	1.91	46	286
4	132	27	7.1	47	91
5	336	28	8.55	48	31
6	10	29	1.5	49	590
7	13	30	139	50	154
8	26	31	14	51	118
9	3.8	32	36	52	350
10	171	33	56	53	154

Table 1 (continued)

Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
11	431	34	803	55	2
12	1.18	35	1773	56	360
13	15	36	2640	59	690
14	4.5	37	520	60	707
15	15	38	207		
16	32	39	235		
17	3.5	40	814		
18	172	41	7.6		
19	2.9	42	286		
20	3315	43	29		
22	2.8	44	2285		

Claims

1. A compound of Formula (I):



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,
R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,
R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, alkoxycarbonylalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl having at least two carbon atoms, alkoxy having at least two carbon atoms, hydroxyalkyl having at least two carbon atoms,
R^5 is hydrogen, halogen, alkyl,
Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and
R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen;
with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or
(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or
(iii) Ar is heteroaryl, or
(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then

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

2. The compound according to claim 1, wherein R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

3. The compound according to claim 2, wherein R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

4. The compound according to claim 1, wherein Ar is heteroaryl.

5. The compound according to claim 4, wherein R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

6. The compound according to claim 1, wherein R^1 is hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen, and Ar is other than phenyl that is ortho-substituted by hydroxy or alkoxy.

7. The compound according to claim 6, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

8. The compound according to claim 1, wherein at least one of R^6 and R^7 is aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom in at least one position.

9. The compound according to claim 8, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

10. The compound according to any one of claims 1 to 9, wherein R^1 is hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

11. The compound according to any one of claims 1 to 10, wherein R^2 and R^3 independently are hydrogen, hydroxy or hydroxymethyl.

12. The compound according to any one of claims 1 to 10, wherein R^4 is hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyi, amino, azido, cyanoalkyl, carboxy or carboxyalkyl.

13. The compound according to claim 12, wherein R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethylaminoethyl.

14. The compound according to any one of claims 1 to 13, wherein R^5 is hydrogen.

15. The compound according to any one of claims 1 to 14, wherein each of R^6 and R^7 independently signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group such as C_{1-8}alkyl, especially C_{1-6}alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms.

16. The compound according to any one of claims 1 to 14, wherein R^6 and R^7 taken together form a ring with the

amine nitrogen.

17. The compound according to any one of claims 1 to 16, wherein at least one of R^6 and R^7 comprises a branched carbon chain.

18. The compound according to any one of claims 1 to 17, wherein Ar is thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl or methylpyrryl.

19. The compound according to claim 1, which is:

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

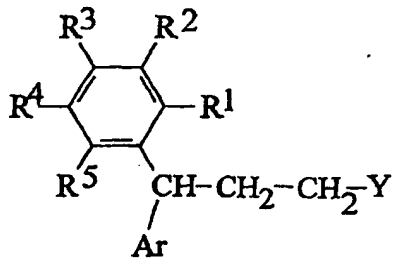
20. The compound according to any one of claims 1 to 19 for use as a pharmaceutically active substance, especially as an anticholinergic agent.

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

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

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

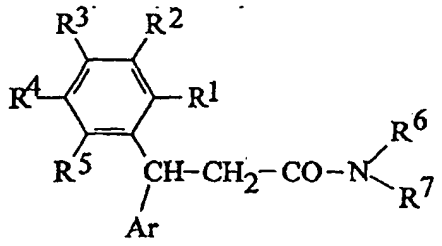
a) reacting a compound of Formula II



II

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

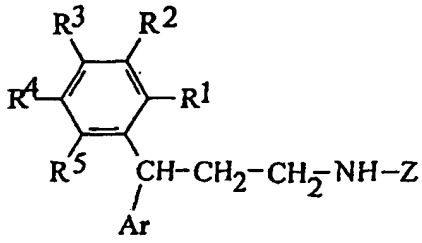
b) reducing a compound of Formula III



III

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

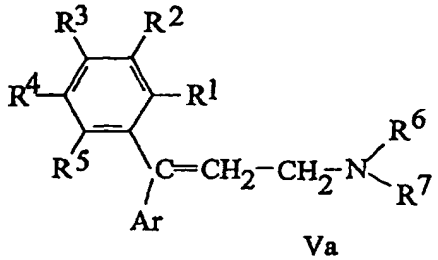
c) N-alkylating a secondary amine of Formula IV



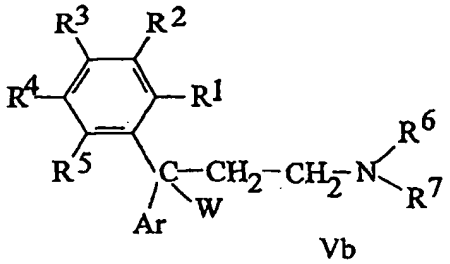
IV

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

d) reducing a compound of Formula Va or Vb



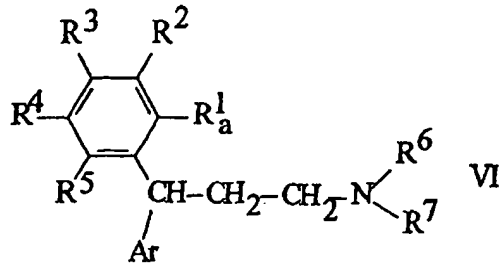
Va



Vb

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

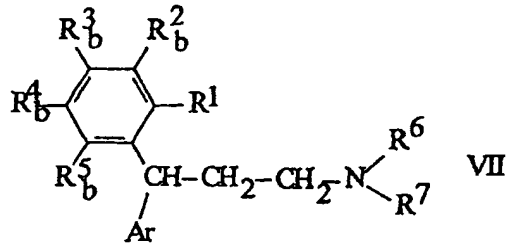
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined in claim 1, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

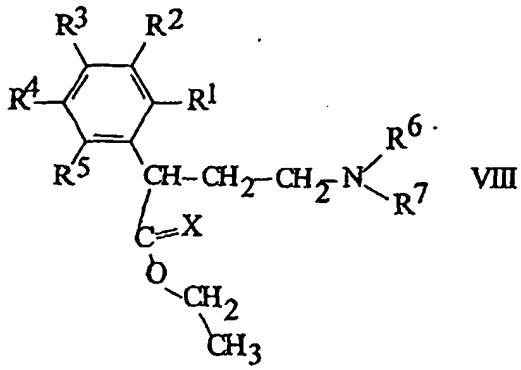


VII

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

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

h) reacting a compound of Formula VIII

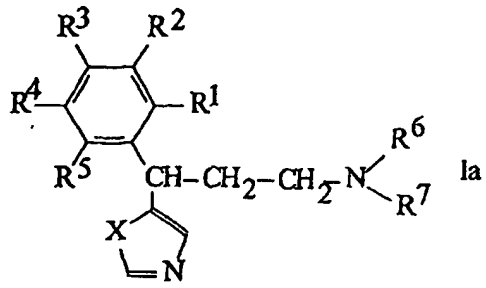


VIII

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

$CH_3N{=}C$: IX

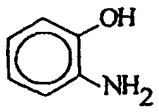
to form a compound of Formula Ia



Ia

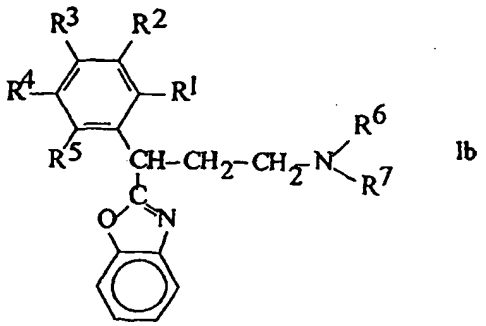
wherein R^1 to R^7 and X are as defined above, or

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



X

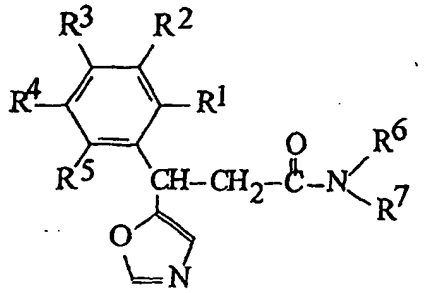
to form a compound of Formula Ib



Ib

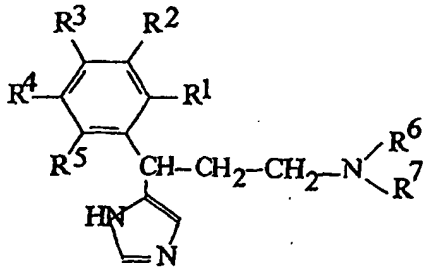
wherein R^1 to R^7 are as defined in claim 1, or

j) converting a compound of Formula XI



XI

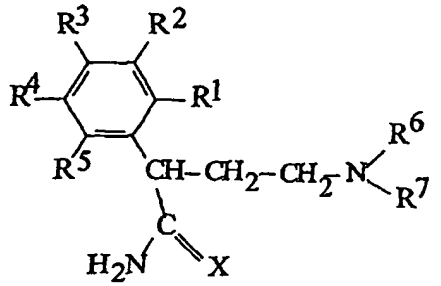
wherein R^1 to R^7 are as defined in claim 1, to a compound of Formula XII



XII

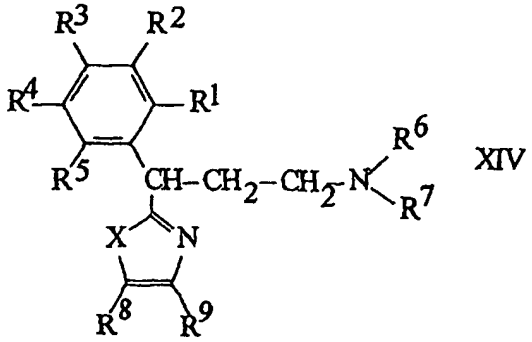
wherein R^1 to R^7 are as defined in claim 1, or

k) converting a compound of Formula XIII



XIII

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



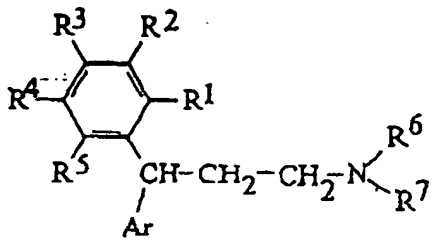
XIV

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

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

Patentansprüche

1. Eine Verbindung der Formel (I);



worin:

R^1 Wasserstoff, Hydroxyl, Alkyl, Alkoxy, Hydroxyalkyl, Trifluormethyl, Amino, Alkylcarbonylamino, Alkylcarbonyloxy, Halogen ist,

R^2 und R^3 unabhängig voneinander Wasserstoff, Hydroxy, Alkyl, Alkoxy, Hydroxyalkyl, Halogen, Alkoxycarbonylalkyl, Carbamoyl, Sulfamoyl sind,

R^4 ω-Hydroxyalkoxy, ω-Aminoalkoxy, ω-Aminoalkylamino, Alkoxyalkyl, Hydroxyalkoxyalkylaminoalkyl, Alkoxycarbonylalkyl, Dihydroxyalkyl, Formyl, Alkylcarbonyl, Alkoxycarbonylalkyl, Alkylcarbonylaminoalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Carbamoylalkyl, Carboxamidoalkyl, Carboxyl, Amino, Nitro, Cyano, Nitrilo, Cyanoalkyl, Azido, Alkyl mit wenigstens zwei Kohlenstoffatomen, Alkoxy mit wenigstens zwei Kohlenstoffatomen, Hydroxyalkyl mit wenigstens zwei Kohlenstoffatomen ist,

R^5 Wasserstoff, Halogen, Alkyl ist,

Ar Aryl oder Heteroaryl ist, welches mono- oder unabhängig disubstituiert sein kann mit Alkyl, Alkoxy, Hydroxy, Hydroxyalkyl, Halogen, Alkoxycarbonylalkyl, Carbamoyl, Sulfamoyl, und

R^6 und R^7 Hydrocarbylgruppen sind, welche gleich oder verschieden sein können, die zusammen wenigstens

drei Kohlenstoffatome enthalten und welche eine oder mehrere Hydroxygruppen tragen können, und wobei die Kohlenstoffatome durch Sauerstoffatome miteinander verbunden sein können und wobei R^6 und R^7 zusammen mit dem Aminstickstoff einen Ring bilden können; unter den Vorbehalten, dass (a) wenn:

(i) wenigstens zwei von R^2, R^3 und R^5 von Wasserstoff verschieden sind oder

(ii) R^1 von Hydroxy oder Methoxy verschieden ist und Ar von Phenyl, das durch Hydroxy oder Methoxy ortho-substituiert ist, verschieden ist oder

(iii) Ar Heteroaryl ist oder

(iv) wenigstens einer von R^6 und R^7 ein aromatisches Hydrocarbyl oder Cycloalkyl ist, dann

R^4 ebenfalls Wasserstoff, Methyl, Methoxy, Hydroxymethyl, Hydroxy, Halogen, Carbamoyl, Sulfamoyl sein kann;
und (b) wenn Ar ein unsubstituiertes Phenyl ist, dann R^1, R^2, R^3, R^4 und R^5 nicht alle Wasserstoff sein können;

deren Salze mit physiologisch verträglichen Säuren und, wenn die Verbindungen in Form von optischen Isomeren vorliegen können, die racemische Mischung der einzelnen Enantiomere.

2. Die Verbindung gemäß Anspruch 1, wobei R^4 ω-Hydroxyalkoxy, ω-Aminoalkoxy, ω-Aminoalkylamino, Alkoxyalkyl, Hydroxyalkoxyalkylaminoalkyl, Dihydroxyalkyl, Formyl, Alkylcarbonyl, Alkoxycarbonyl, Alkoxycarbonylalkyl, Alkylcarbonylaminoalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Carbamoylalkyl, Carboxamidoalkyl, Carboxyl, Amino, Nitro, Cyano, Nitrilo, Cyanoalkyl oder Azido ist.

3. Die Verbindung gemäß Anspruch 2, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind, und Ar Phenyl oder Phenyl, welches mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

4. Die Verbindung gemäß Anspruch 1, wobei Ar Heteroaryl ist.

5. Die Verbindung gemäß Anspruch 4, wobei R^1 Wasserstoff oder Methyl ist und R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind.

6. Die Verbindung gemäß Anspruch 1, wobei R^1 Wasserstoff, Alkyl, Hydroxyalkyl, Trifluormethyl, Amino, Alkylcarbonylamino, Alkylcarbonyloxy oder Halogen ist und Ar von Phenyl, das durch Hydroxy oder Alkoxy ortho-substituiert ist, verschieden ist.

7. Die Verbindung gemäß Anspruch 6, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen Wasserstoff sind, und Ar Phenyl oder Phenyl, welches mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

8. Die Verbindung gemäß Anspruch 1, wobei wenigstens einer von R^6 und R^7 ein aromatisches Hydrocarbyl, Cydoalkyl oder eine Hydrocarbylkette ist, wobei die Kohlenstoffatome über ein Sauerstoffatom in wenigstens einer Position miteinander verbunden sind.

9. Die Verbindung gemäß Anspruch 8, wobei R^1 Wasserstoff oder Methyl ist, R^2, R^3, R^4 und R^5 entweder alle Wasserstoff sind oder einer von R^2, R^3, R^4 und R^5 Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen ist und die anderen WasserStoff sind, und Ar Phenyl oder Phenyl, das mit Methyl, Methoxy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen mono- oder unabhängig disubstituiert ist, ist.

10. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 9, wobei R^1 Hydroxy, Halogen, Trifluormethyl, Amino, Methoxy oder Hydroxymethyl ist

11. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 10, wobei R^2 und R^3 unabhängig voneinander Wasser-

stoff, Hydroxy oder Hydroxymethyl sind.

12. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 10, wobei R^4 WasserStoff, Formyl, Alkoxycarbonyl, Alkylcarbonyl, Hydroxyalkyl, Alkoxyalkyl, Carboxamidoalkyl, Carbamoylalkyl, Aminoalkyl, Amino, Azido, Cyanoalkyl, Carboxy oder Carboxyalkyl ist.

13. Die Verbindung gemäß Anspruch 12, wobei R^4 Wasserstoff, Formyl, Hydroxymethyl, Hydroxyethyl, Hydroxypropyl, Hydroxybutyl, Hydroxypentyl, Hydroxyhexyl, Ethoxymethyl, Methoxycarbonyl, Amino, Aminopropyl, Acetyl, 1,2-Hydroxyethyl, Ethylaminomethyl oder Hydroxyethoxyethylaminoethyt ist.

14. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 13, wobei R^5 Wasserstoff ist.

15. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 14, wobei jeder von R^6 und R^7 unabhängig voneinander eine gesättigte Hydrocarbylgruppe, insbesondere eine gesättigte aliphatische Hydrocarbylgruppe wie z. B. ein C_{1-8}-Alkyl, insbesondere ein C_{1-6}-Alkyl, oder Adamantyl bedeutet, wobei R^6 und R^7 zusammen wenigstens drei, vorzugsweise wenigstens vier Kohlenstoffatome enthalten.

16. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 14, wobei R^6 und R^7 zusammengenommen mit dem Aminstickstoff einen Ring bilden.

17. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 16, wobei wenigstens einer von R^6 und R^7 eine verzweigte Kohlenstoffkette umfasst.

18. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 17, wobei Ar Thienyl, Pyrryl, Thiazolyl, Oxazolyl, Methylthiazolyl oder Methylpyrryl ist.

19. Die Verbindung gemäß Anspruch 1, welche

N,N-Diisopropyl-3-(2-fluorphenyl)-3-phenylpropanaminhydrochlorid,
N,N-Diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamin oder dessen 3(R)-Isomer,
N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen 1(S*)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamin oder dessen (R)-Isomer,
N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamin oder dessen (R)-Isomer,
N-Cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamin,
N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamin oder
N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamin oder dessen (R)-Isomer ist.

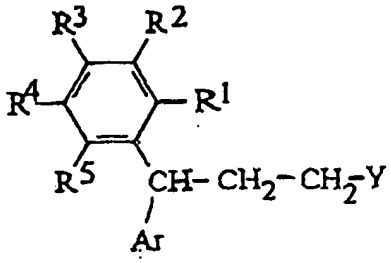
20. Die Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 zur Verwendung als eine pharmazeutisch aktive Substanz, insbesondere als ein anticholinerges Mittel.

21. Eine pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 und vorzugsweise einen kompatiblen pharmazeutischen Träger.

22. Verwendung einer Verbindung gemäß irgendeinem der Ansprüche 1 bis 19 zur Herstellung eines anticholinergen Arzneimittels.

23. Ein Verfahren zur Herstellung einer Verbindung gemäß irgendeinem der Ansprüche 1 bis 19, welches umfasst:

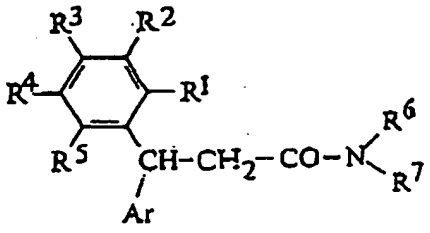
a) Umsetzen einer Verbindung der Formel II



II

worin R^1 bis R^5 und Ar wie in Anspruch 1 definiert sind und Y eine Abgangsgruppe ist, mit einem Amin HNR^6R^7, wobei R^6 und R^7 wie oben definiert sind, oder

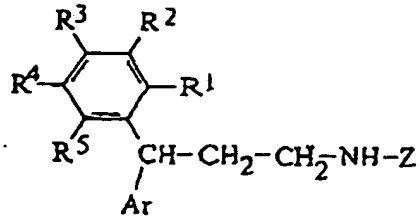
b) Reduzieren einer Verbindung der Formel III



III

worin R^1 bis R^7 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, oder

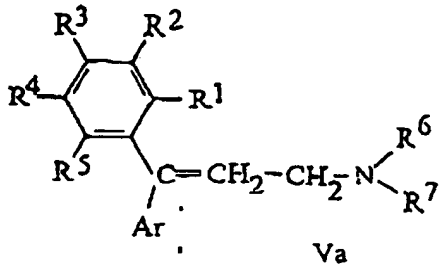
c) N-Alkylieren eines sekundären Amins der Formel IV



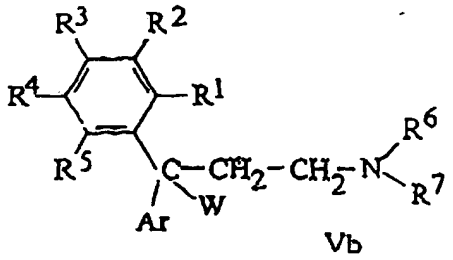
IV

worin R^1 bis R^5 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, und worin Z dieselbe Bedeutung wie R^6 und R^7 aufweist, oder

d) Reduzieren einer Verbindung der Formel Va oder Vb



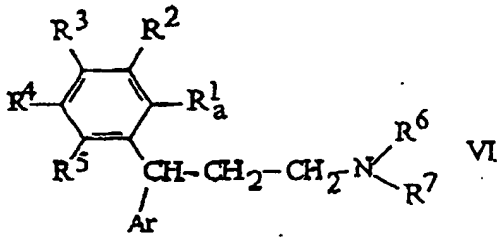
Va



Vb

worin R^1 bis R^7 und Ar wie in Anspruch 1 definiert sind und alle Hydroxygruppen geschützt sein können, und W eine Hydroxygruppe oder Halogen bedeutet, oder

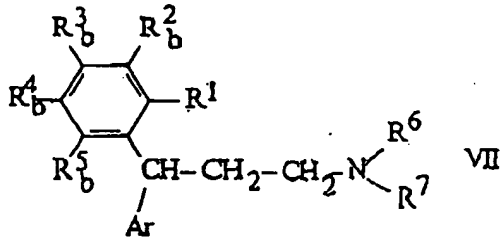
e) bei einer Verbindung der Formel VI



VI

worin R^2 bis R^7 und Ar wie in Anspruch 1 definiert sind und R^1a Carboxyl oder Alkoxy ist, Umwandeln von R^1a in Hydroxy oder

f) bei einer Verbindung der Formel VII

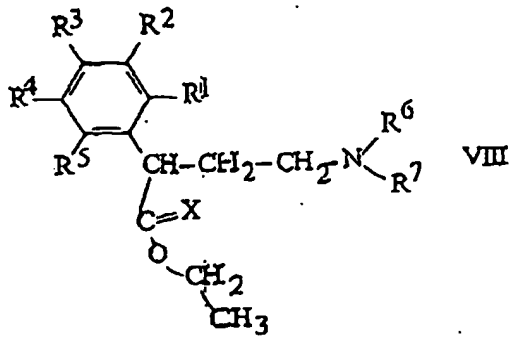


VII

worin R^1, R^6, R^7 und Ar wie in Anspruch 1 definiert sind und einer von $R^2{}_b$ bis $R^5{}_b$ Alkylen ist und die anderen wie in Anspruch 1 wie für R^2 bis R^5 definiert sind, Reduzieren von Alkylen zu Alkyl, Hydroxyalkyl oder Dihydroxyalkyl oder

g) bei einer Verbindung der Formel I wie in Anspruch 1 definiert, Umwandeln von einer oder mehreren der Gruppen R^1 bis R^5 in eine andere oder andere Gruppen R^1 bis R^5 oder

h) Umsetzen einer Verbindung der Formel VIII

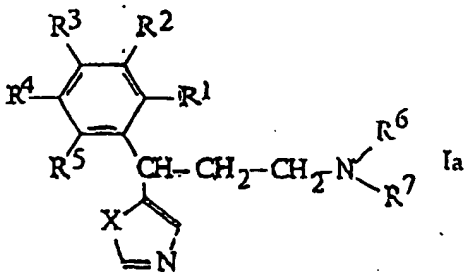


VIII

worin R^1 bis R^7 wie in Anspruch 1 definiert sind und X Sauerstoff oder Schwefel ist, mit einer Verbindung der Formel IX

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

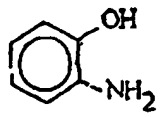
um eine Verbindung der Formel Ia



Ia

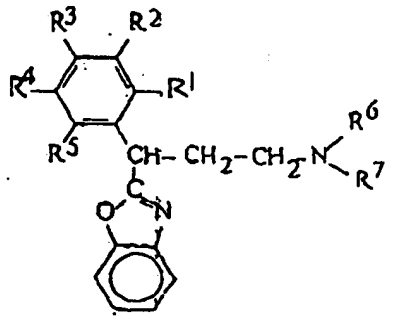
zu bilden, worin R^1 bis R^7 und X wie oben definiert sind, oder

i) Umsetzen einer Verbindung der Formel VIII oben, worin X Sauerstoff ist, mit einer Verbindung der Formet X



X

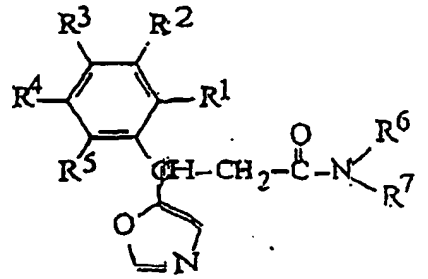
um eine Verbindung der Formel Ib



Ib

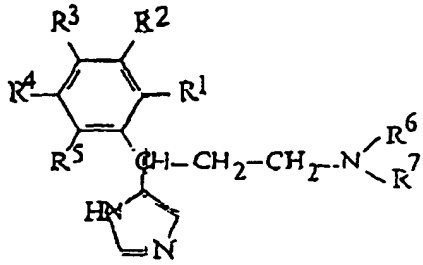
zu bilden, worin R^1 bis R^7 wie in Anspruch 1 definiert sind, oder

j) Umwandeln einer Verbindung der Formel XI



XI

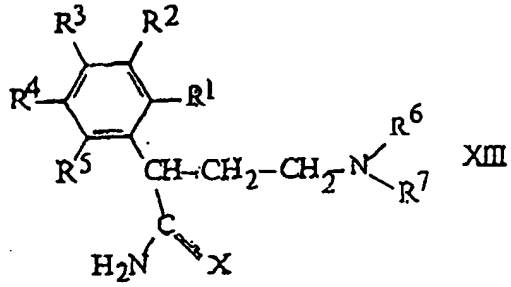
worin R^1 bis R^7 wie in Anspruch 1 definiert sind, in eine Verbindung der Formel XII



XII

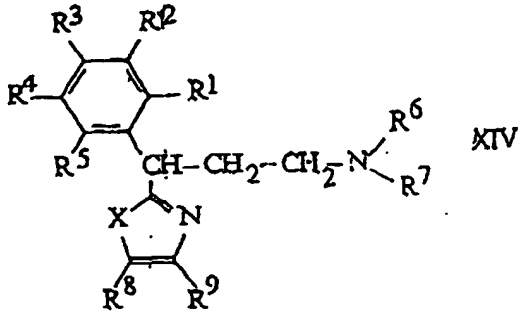
worin R^1 bis R^7 wie in Anspruch 1 definiert sind, oder

k) Umwandeln einer Verbindung der Formel XIII



XIII

worin R^1 bis R^7 wie in Anspruch 1 definiert sind und X Sauerstoff oder Schwefel ist, in eine Verbindung der Formel XIV



XIV

worin R^1 bis R^7 und X wie oben definiert sind und R^8 und R^9 unabhängig voneinander Wasserstoff oder Alkyl sind, und

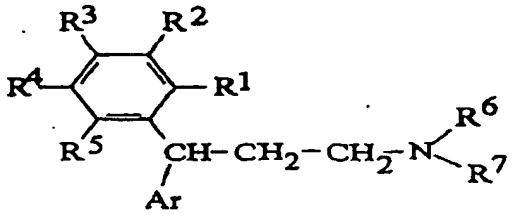
i) wenn nötig, Abspalten der Hydroxyschutzgruppen in den erhaltenen Verbindungen,

ii) wenn gewünscht, Umwandeln der erhaltenen Basen der Formel I in deren Salze mit physiologisch verträglichen Säuren, oder umgekehrt, und/oder

iii) wenn gewünscht, Auftrennen einer erhaltenen Mischung von optischen Isomeren in die einzelnen Enantiomeren.

Revendications

1. Composé de Formule I :



Formule I

dans laquelle :

R^1 est hydrogène, hydroxy, alkyle, alkoxy, hydroxyalkyle, trifluorométhyle, amino, alkylcarbonylamino, alkylcarbonyloxy, halogène,
R^2 et R^3 sont indépendamment hydrogène, hydroxy, alkyle, alkoxy, hydroxyalkyle, halogène, alkoxycarbonylalkyle, carbamoyle, sulphamoyle,
R^4 est ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyle, hydroxyalkoxyalkylaminoalkyle, alkoxycarbonylalkyle, dihydroxyalkyle, formyle, alkylcarbonyle, alkoxycarbonylalkyle, alkylcarbonylaminoalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxylalkyle, carbamoylalkyle, carboxamidoalkyle, carboxyle, amino, nitro, cyano, nitrilo, cyanoalkyle, azido, un alkyle ayant au moins deux atomes de carbone, un alkoxy ayant au moins deux atomes de carbones, un hydroxyalkyle ayant au moins deux atomes de carbones,
R^5 est hydrogène, halogène, alkyle,
Ar est un aryle ou un hétéroaryle pouvant être mono- ou indépendamment di-substitué par un alkyle, alkoxy, hydroxy, hydroxyalkyle, halogène, alkoxycarbonylalkyle, carbamoyle, sulphamoyle, et
R^6 et R^7 sont des groupes hydrocarbyles pouvant être identiques ou différents, contenant ensemble au moins trois atomes de carbone, et pouvant porter un ou plusieurs groupes hydroxy, dans lesquels les atomes de carbones peuvent être interconnectés par des atomes d'oxygène, et dans laquelle R^6 et R^7 peuvent former un cycle avec l'azote aminé ; à la condition que (a) lorsque :

(i) au moins deux des éléments R^2, R^3 et R^5 sont autres qu'hydrogène, ou
(ii) R^1 est autre qu'hydroxy ou méthoxy, et Ar est autre qu'un phényle ortho-substitué par hydroxy ou méthoxy, ou
(iii) Ar est un hétéroaryle, ou
(iv) au moins un des éléments R^6 et R^7 est un cycloalkyle ou un hydrocarbyle aromatique, alors

R^4 peut être hydrogène, méthyle, méthoxy, hydroxyméthyle, hydroxy, halogène, carbamoyle, sulphamoyle;

et à la condition que (b), lorsque :

Ar est un phényle non substitué, alors R^1, R^2, R^3, R^4 et R^5 ne peuvent tous être des atomes d'hydrogène ; leurs sels avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous la forme d'isomères optiques, le mélange racémique et les énantiomères individuels.

2. Composé selon la revendication 1, dans lequel R^4 est ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyle, hydroxyalkoxyalkylaminoalkyle, dihydroxyalkyle, formyle, alkylcarbonyle, alkoxycarbonyle, alkoxycarbonylalkyle, alkylcarbonylaminoalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxylalkyle, carbamoylalkyle, carboxamidoalkyle, carboxyle, amino, nitro, cyano, nitrilo, cyanoalkyle ou azido.

3. Composé selon la revendication 2, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle, ou halogène et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono ou indépendamment disubstitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène.

4. Composé selon la revendication 1, dans lequel Ar est un hétéroaryle.

5. Composé selon la revendication 4 dans lequel R^1 est hydrogène ou méthyle, et soit R^2, R^3, R^4 et R^5 sont tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène.

6. Composé selon la revendication 1, dans lequel R^1 est hydrogène, alkyke, hydroxyalkyle, trifluorométhyle, amino, alkylcarbonylamino, alkylcarbonyloxy ou halogène, et Ar est autre qu'un phényle ortho-substitué par hydroxy ou alkoxy.

7. Composé selon la revendication 6, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3, R^4 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono- ou indépendamment di-substitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou

halogène.

8. Composé selon la revendication 1, dans lequel au moins un des éléments R^6 et R^7 est un cycloalkyle, un hydrocarbyle aromatique ou une chaîne hydrocarbyle dans laquelle les atomes de carbone sont interconnectés par des atomes d'oxygène en au moins une position.

9. Composé selon la revendication 8, dans lequel R^1 est hydrogène ou méthyle, R^2, R^3, R^4 et R^5 sont soit tous des atomes d'hydrogène, soit un des éléments R^2, R^3, R^4 et R^5 est méthyle, méthoxy, hydroxy, carbamoyle, sulphamoyle ou halogène, et les autres sont des atomes d'hydrogène, et Ar est un phényle ou un phényle mono- ou indépendamment di-substitué par méthyle, méthoxy, hydroxy, hydroxyméthyle, carbamoyle, sulphamoyle ou halogène.

10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel R^1 est hydroxy, halogène, trifluorométhyle, amino, méthoxy ou hydroxyméthyle.

11. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R^2 et R^3 sont indépendamment hydrogène, hydroxy, ou hydroxyméthyle.

12. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R^4 est hydrogène, formyle, alkoxycarbonyle, alkylcarbonyle, hydroxyalkyle, alkoxyalkyle, carboxamidoalkyle, carbamoylalkyle, aminoalkyle, amino, azido, cyanoalkyle, carboxy ou carboxyalkyle.

13. Composé selon la revendication 12, dans lequel R^4 est hydrogène, formyle, hydroxyméthyle, hydroxyéthyle, hydroxypropyle, hydroxybutyle, hydroxypentyle, hydroxyhexyl, éthoxyméthyle, méthoxycarbonyle, amino, aminopropyle, acétyle, 1,2-hydroxyéthyle, éthylaminométhyle, ou hydroxyéthoxy-éthylaminoéthyle.

14. Composé selon l'une quelconque des revendications 1 à 13, dans lequel R^5 est hydrogène.

15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel chacun des éléments R^6 et R^7 désigne indépendamment un groupe hydrocarbyle saturé, en particulier un groupe hydrocarbyle aliphatique saturé tel qu'un alkyle de C_1 à C_8, plus particulièrement un adamantyl ou un alkyle de C_1 à C_6, R^6 et R^7 contenant ensemble au moins trois, de préférence quatre, atomes de carbone.

16. Composé selon l'une quelconque des revendications 1 à 14, dans lequel R^6 et R^7, pris ensemble, forment un cycle avec l'azote aminé.

17. Composé selon l'une quelconque des revendications 1 à 16, dans lequel au moins un des éléments R^6 et R^7 comprend une chaîne de carbone ramifiée.

18. Composé selon l'une quelconque des revendications 1 à 17, dans lequel Ar est thiényl, pyrryl, thiazolyl, oxazolyl, méthylthiazolyl ou méthypyrryl.

19. Composé selon la revendication 1, qui est :

N,N-diisopropyl-3-(2-fluorophényl)-3-phénylpropanamine chlorhydrate,
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(2-hydroxy-5-méthyloxycarbonyl-phényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-acétyl-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyéthyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyéthyl)-phényl]-3-phénylpropanamine, ou son isomère 3 (R),
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyéthyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère 1 (S*),
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyphéxyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-éthoxyméthyl-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(3-acétamidopropyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[5-(2-cyanoéthyl)-2-hydroxyphényl]-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-(5-amino-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),

N,N-diisopropyl-3-(5-azido-2-hydroxyphényl)-3-phénylpropanamine, ou son isomère (R),
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phényl]-3-phénylpropanamine, ou son isomère (R),
N-cyclobutyl-N-méthyl-3-(2-hydroxyphényl)-3-phénylpropanamine,
N,N-diisopropyl-3-(2-hydroxyphényl)-3-(2-thiényl) propanamine, ou
N,N-diisopropyl-3-(2-hydroxy-5-méthylphényl)-3-(2-thiényl) propanamine, ou son isomère (R).

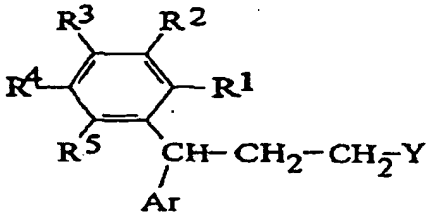
20. Composé selon l'une quelconque des revendications 1 à 19, pour utilisation dans une substance pharmaceutiquement active, en particulier un agent anticholinergique.

21. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 19, et de préférence un véhicule pharmaceutique compatible.

22. Utilisation d'un composé selon l'une quelconque des revendications 1 à 19 pour la préparation d'un médicament anticholinergique.

23. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 19, qui comprend :

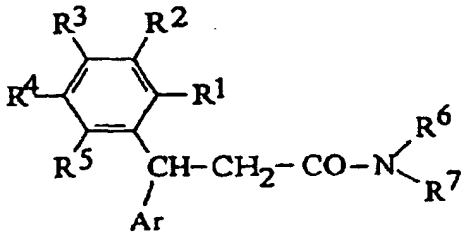
a) la réaction d'un composé de Formule II



Formule II

dans laquelle R^1 à R^5 et Ar sont tels que définis dans la revendication 1, et Y est un groupe partant, avec une amine HNR^6, R^7, dans laquelle R^6 et R^7 sont tels que définis ci-dessus, ou

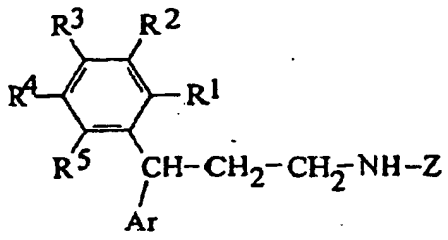
b) la réduction d'un composé de Formule III



Formule III

dans laquelle R^1 à R^7 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, ou

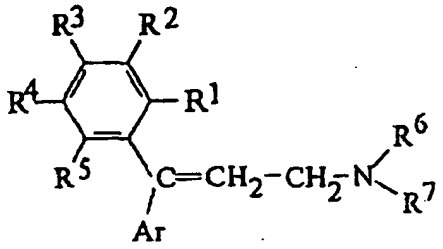
c) la N-alkylation d'une amine secondaire de Formule IV



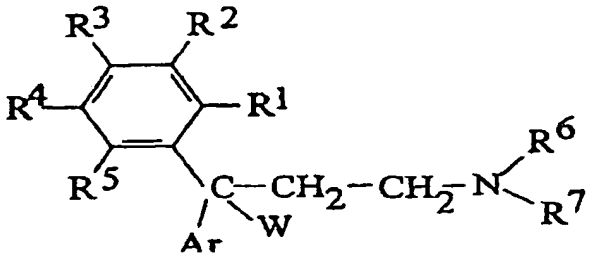
Formule IV

dans laquelle R^1 à R^5 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, et dans laquelle Z a la même signification que R^6 et R^7, ou

d) la réduction d'un composé de Formule Va ou Vb



Formule Va



Formule Vb

dans laquelle R^1 à R^7 et Ar sont tels que définis dans la revendication 1 et tout groupe hydroxy peut être protégé, et dans laquelle W désigne un groupe hydroxy ou halogène, ou

e) dans un composé de Formule VI