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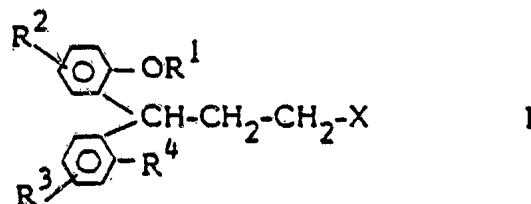
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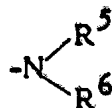
(57) It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute toxicity.

CLAIM

1. 3,3-Diphenylpropylamines of formula I



wherein R¹ signifies hydrogen or methyl, R², R³ and R⁴ independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



wherein R⁵ and R⁶ may carry one or more hydroxy groups and/or signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and

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wherein R⁵ and R⁶ 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.

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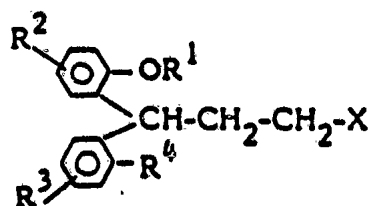
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(22) International Filing Date: 20 January 1989 (20.01.89)**(74) Agents:** KUMMELSTEN, Per, Arne et al.; Uppsala Patentbyrå, Box 9013, S-750 09 Uppsala (SE).**(31) Priority Application Number:** 8800207-6**(32) Priority Date:** 22 January 1988 (22.01.88)**(33) Priority Country:** SE**(81) Designated States:** AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.**(71) Applicant (for all designated States except US):** KABIV-ITRUM AB [SE/SE]; Lindhagensgatan 133, S-112 87 Stockholm (SE).**Published***With international search report.***(72) Inventors; and****(75) Inventors/Applicants (for US only):** JÖNSSON, Nils, Åke [SE/SE]; Fotbollsvägen 6, S-151 59 Södertälje (SE). SPARF, Bengt, Åke [SE/SE]; Drottningvägen 14A, S-142 00 Trångsund (SE). MIKIVER, Lembit [SE/SE]; Badstigen 6, S-153 00 Järna (SE). MOSES, Pinchas [SE/SE]; Dalvägen 6, S-132 00 Saltsjö-Boo (SE). NILVEBRANT, Lisbet [SE/SE]; Fältmarskalksvägen 9, S-161 35 Bromma (SE). GLAS, Gunilla [SE/SE];

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(54) Title: NEW AMINES, THEIR USE AND PREPARATION**(57) Abstract**

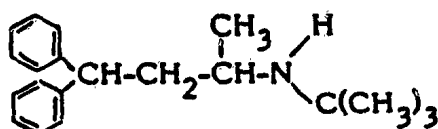
Novel 3,3-diphenylpropylamines of formula (I) wherein R¹ signifies hydrogen or methyl, R², R³ and R⁴ independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group -NR⁵, R⁶, wherein R⁵ and R⁶ signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and which 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, their use as drugs, especially as anticholinergic agents, their use for preparing an anticholinergic drug, pharmaceutical compositions containing the novel amines, and methods for preparing the same.

New amines, their use and preparation.

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. 215 499 discloses certain 3,3-diphenylpropylamines 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

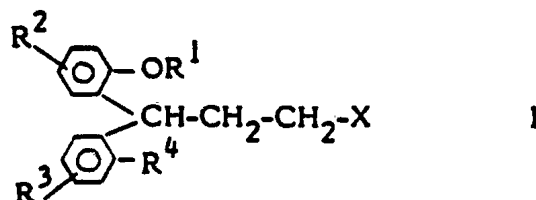


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect 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



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 hydrocarbon groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and wherein R^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom than the amine nitrogen.

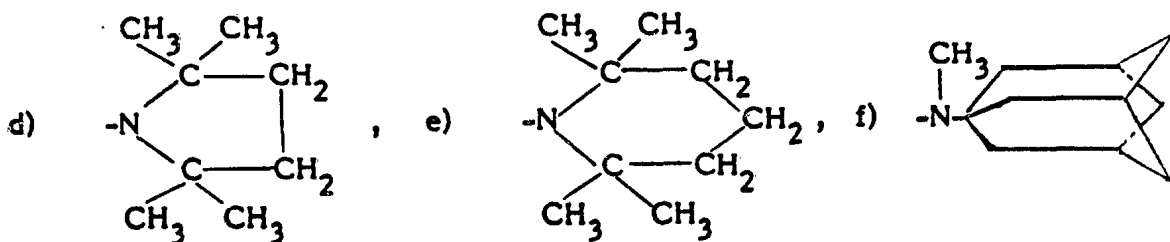
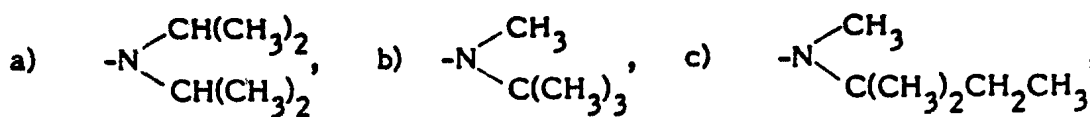
The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

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

A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8} -alkyl, especially C_{1-6} -alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino-groups X in formula I include the

following groups a) - f), each of which may carry one or more hydroxy groups.



The following are examples of presently preferred specific compounds of formula I:

5

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,

10

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,

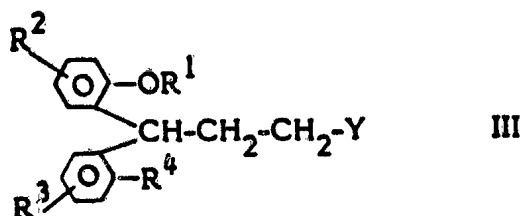
N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,

15

N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine

In a second aspect the invention provides methods for preparing the compounds of formula I, especially the following methods:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III



20

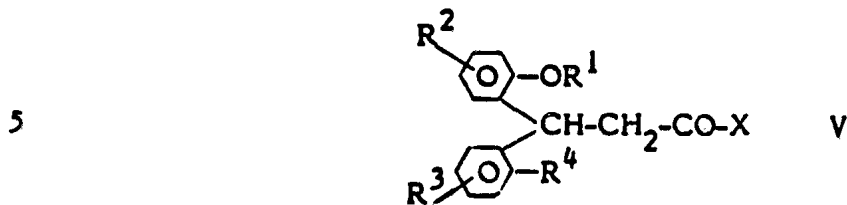
wherein R^1 - R^4 are as defined above, and any hydroxy groups may be protected such as by methylation or benzylation, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group,

with an amine of formula IV



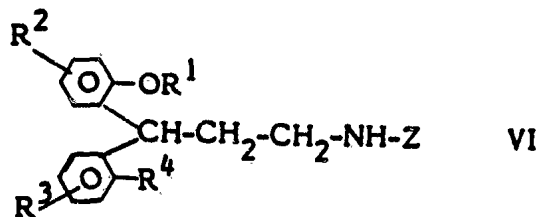
wherein X is as defined above, or

b) reducing a 3,3-diphenylpropionamide of formula V



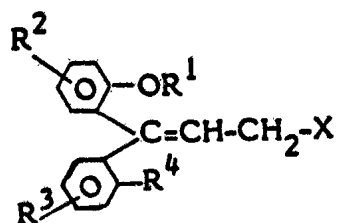
wherein $\text{R}^1\text{-R}^4$ and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride,

c) N-methylating a secondary 3,3-diphenylpropylamine VI

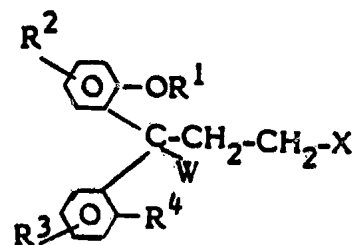


10 wherein $\text{R}^1\text{-R}^4$ are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

15 d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein $\text{R}^1\text{-R}^4$ 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

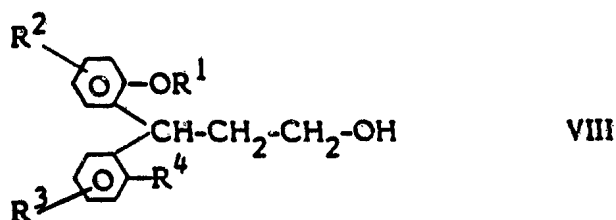
- 5
- i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or
- ii) if desired converting obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, 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 R¹ is hydrogen and/or R⁴ is hydroxy.

10 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.

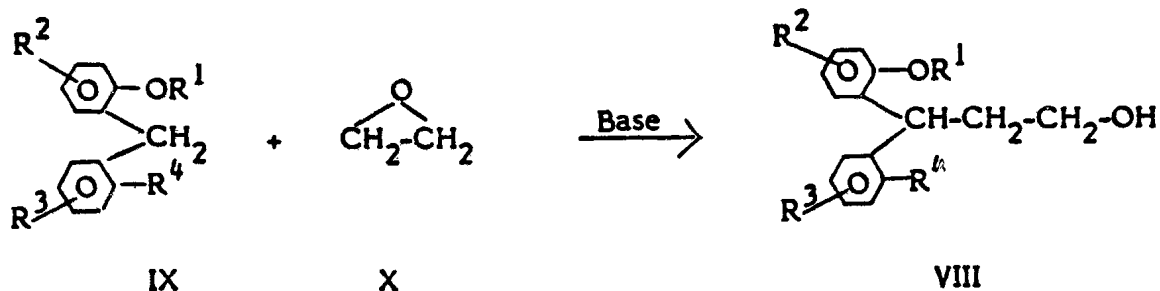
15 The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

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.

20 Novel compounds of formula VIII



25 wherein R¹-R⁴ 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 oxidé (X) to a correspondingly substituted diphenylmethane (IX) in the presence of a suitable base such as sodium amide:

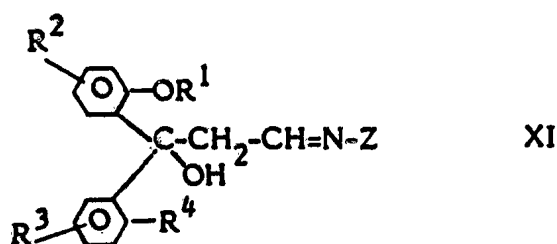


The compounds VIII can also be prepared by reduction of the corresponding 3,3-diphenylpropionic acids, preferably using complex metal hydrides.

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 $\text{H}_2\text{N-Z}$ (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



wherein $\text{R}^1\text{-R}^4$ 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.

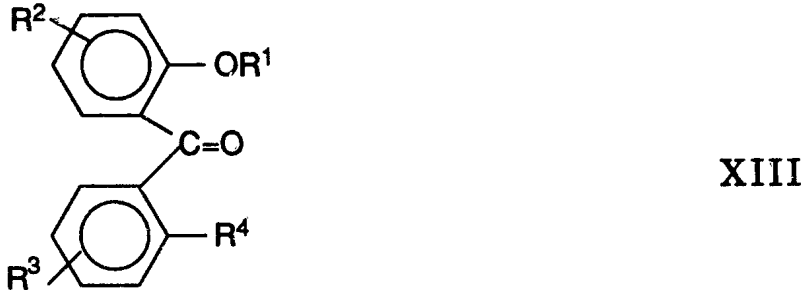
The unsaturated hydroxy amines XI can conveniently be prepared by the

addition of a Schiff base of formula XII



wherein Z is as defined above,

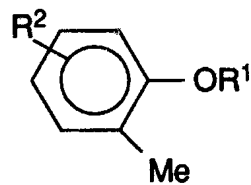
to a benzophenone of formula XIII



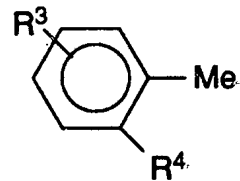
5

wherein R¹-R⁴ 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
10 XIVa or XIVb

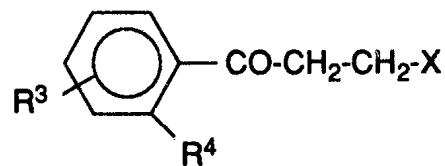


XIVa



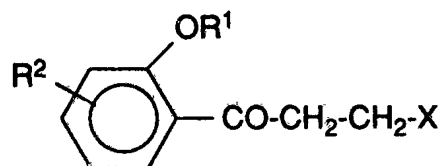
XIVb

to a ketoamine



XVa

or



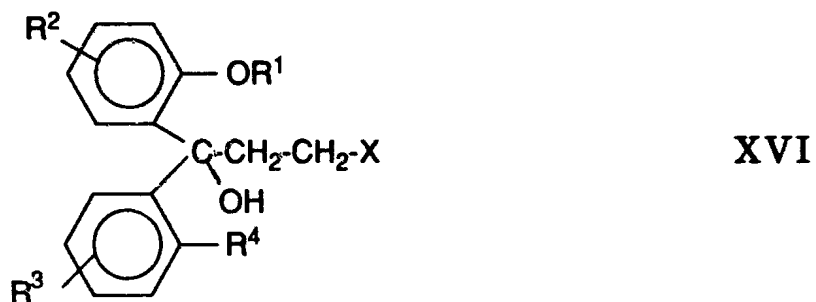
XVb

15



7a

respectively to form a corresponding hydroxy amine XVI



and, if desired, splitting off water from compound XVI.

- 5 In formulae XVIa, XVIb, XVa, XVb, XVI, R¹-R⁴ are as defined above, and Me signifies 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
10 like, in accordance with accepted pharmaceutical procedures. Such pharmaceuti-

cal 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

¹H-NMR spectra were run in CDCl₃ using a JEOL PMX60 spectrometer.
5 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:

10 IPE = diisopropyl ether
PET = petroleum ether
Ether = diethyl ether

Amines are abbreviated as follows:

IPA = diisopropyl amine
15 TBA = tert.butyl amine

Melting points were taken on a Kofler bench.

Temperatures are in °C.

Water is used for the washing steps, unless otherwise stated.

Example 1

20 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
25 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

30 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

5 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

10 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).

15 $C_{15}H_{12}O_3$ (240.2) requires: C 74.99 H 5.04 O 19.98
Found 75.0 5.01 19.9

20 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

25 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.

30 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).

35 $C_{18}H_{20}O$ (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).

5 $C_{30}H_{28}O_4$ (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.

10 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.

15

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.

20

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.

25

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.

30

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

35

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 carbonate 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
20 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 LiAlH₄ (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).

35 c) 3-(2,3-Dibenzoyloxyphenyl)-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).

5 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).

10 $C_{19}H_{24}O_3$ (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).

15 $C_{29}H_{28}O_3$ (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).

20 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-Fluorophenyl)-3-(2-methoxyphenyl)propanol (XXVI)

25 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°.

30 $C_{14}H_{13}FO_2$ (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).

$\text{C}_{16}\text{H}_{17}\text{FO}_2$ (260.3) requires:	C 73.52	H 6.58
Found	74.1	6.77

1) 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° .

$\text{C}_{16}\text{H}_{17}\text{ClO}_2$ (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 $+5^\circ\text{C}$) 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 $< 50^\circ\text{C}$, giving a crude oil in quantitative yield. Recrystallization from IPE gave white crystals of low and indefinite m.p.

$\text{C}_{24}\text{H}_{26}\text{O}_5\text{S}$ (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).

5 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 a similar way in 98% yield from the propanol (XIX) of Example 3d).

10 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

15 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

20 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).

25 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).

30 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-Fluorophenyl)-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
 5 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
 10 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°.

15 $C_{23}H_{24}O_4S$ (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-
 20 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°.

25 $C_{23}H_{23}ClO_4S$ (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),
 30 hydrogen oxalate

The tosylate (XXVII) of Example 4a) (42.6 g, 0.1 mol) in 100 ml aceto-
 nitrile 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
 35 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).

5 $C_{25}H_{35}NO_6$ (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).

10 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. 15 176° (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

20 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

25 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).

30 $C_{25}H_{38}NO_2Cl$ (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).

5 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).

10 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).

15 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

20 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

25 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
30 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-methylpropanol. The solid product was crystallized from diisopropyl ether and melted at 103°C. It was used as start material in Example 7p).

$C_{26}H_{31}NO_2$ (389.5) requires: C 80.17 H 8.02 N 3.60 O 8.22
 Found 80.0 8.09 3.69 8.51

q) N-(1-Adamantyl)-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 1-aminoadamantane. It was used as start material in Example 7q). The hydrochloridesemihydrate was prepared in acetonitrile and melted at 225°C.

$C_{32}H_{37}NO \cdot HCl \cdot 1/2 H_2O$ (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

30 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

5 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

10 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

15 d) N-tert-Butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine
 (LIII), hydrochloride

20 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

25 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

30 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).

35 $C_{23}H_{34}NOCl$ (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).

5 C₃₃H₃₈NO₂Cl (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

10 The free base was obtained in 94% yield from the tosylate (XXXIV) of Example 4h). The HCL-salt had m.p. 210° (acetone-ether).

C₃₅H₄₂NO₂Cl (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

15 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).

C₂₁H₃₀NO₂Cl (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

20 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).

C₂₃H₃₄NO₄Cl (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

25 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).

30 C₂₀H₂₇NO₂Cl (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

5 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

10 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).

15 $C_{24}H_{36}NO_2Cl$ (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

20 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

25 Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

a) N-Methyl-N-tert. butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXV), hydrochloride

30 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°.

35 $C_{21}H_{30}NOCl$ (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).

5 $C_{22}H_{32}NOCl$ (362.0) requires: C 73.00 H 8.91 N 3.87 O 4.42 Cl 9.08
Found 73.0 8.96 3.94 4.59 9.77

c) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxyphenyl)propylamine (LXVII), hydrochloride

10 The free base was obtained in 96% yield from the amine (L) of Example 6a). The HCl-salt had m.p. 187-190° (acetone-ether).

$C_{22}H_{33}NOCl$ (378.0) requires: C 69.91 H 8.54 N 3.71 O 8.47 Cl 9.38
Found 69.9 8.56 3.53 8.93 8.92

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LXVIII)

15 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)

20

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

25 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).

30 $C_{21}H_{29}NOClF$ (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

5 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

10 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).

15 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

20 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

25 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.

30 $C_{24}H_{36}NO_4Cl \cdot 1/4 H_2O$ (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).

35 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-phenylpropyl-amine (LXXVIII)

This was obtained as an oil in 97% yield from the amine (LII) of Example 6c).

5 NMR: 6.9-7.3 (m 14H), 5.0 (s 4H), 4.5 (t 1H), 2.2 (s 3H), 0.9 (s 9H).

o) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropyl-amine

10 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°.

$C_{21}H_{28}ClNO \cdot C_2H_2O_4$ (436.0) requires: C 63.37 H 6.94 N 3.21 Cl 8.13
Found 62.7 6.83 3.10 7.97

15 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).

20 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

25 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 hydrolyzed 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.

30
35

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. $203-204^{\circ}$ (acetone-ether) and seems to be associated with 1/4 mol of water.

10 $\text{C}_{21}\text{H}_{29}\text{NO}_3 \cdot \text{HCl} \cdot 1/4 \text{H}_2\text{O}$ (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)

15 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. $220-22^{\circ}$, and was associated with 1/4 mol of water.

20 $\text{C}_{21}\text{H}_{27}\text{NO}_2 \cdot \text{HCl} \cdot 1/4 \text{H}_2\text{O}$ requires: C 68.82 H 7.86 N 3.82 O 9.82 Cl 9.68
Found 68.8 7.89 3.92 9.81 9.44

c) N-Methyl-N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropyl-amine (LXXXI), hydrogen fumarate

25 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).

$\text{C}_{21}\text{H}_{29}\text{NO}_2 \cdot \text{HCl}$ (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

30 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. $185-190^{\circ}$ (acetone).

$\text{C}_{26}\text{H}_{35}\text{NO}_6$ (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 9Removal of O-protective groupsa) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine
(LXXXII), hydrochloride

5 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 BBr₃ in CH₂Cl₂ (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
10 evaporated, giving a viscous syrup. The HCl-salt had m.p. 222° (methanol-ether), yield 31%.

C₂₁H₂₉NO.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.

15 b) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethyl-
piperidine (LXXXIII), hydrogen fumarate

From the amine (LXIV) of Example 5l). Crude yield 78%. M.p. fumaric acid salt = indefinite.

20 C₂₈H₃₇O₅ (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).

25 C₂₂H₃₁NO.HCl. 1/4 H₂O (366.5) requires: C 72.09 H 8.95 N 3.82 O 5.46 Cl 9.67
Found 72.3 8.95 3.71 5.68 9.61

d) N-Methyl-N-tert.butyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl-
propylamine (LXXXV), hydrochloride

30 From the amine (LXVI) of Example 7b). Crude yield 100%. HCl-salt, m.p. > 260° (ethanol).

C₂₁H₂₉NO.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

35 From the amine (XXXVIII) of Example 5a). Crude yield 57%. HCl-salt, m.p. 257° (ethanol-ether).

$C_{21}H_{29}NO_2 \cdot HCl$ (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

5 From the amine (LXVII) of Example 7c). Crude yield 100%, m.p. 190°. HCl-salt, m.p. 252° (ethanol).

$C_{20}H_{27}NO_2 \cdot HCl$ (349.9) requires: C 68.65 H 8.06 N 4.00 Cl 10.13
 Found 68.4 8.06 4.17 9.59

10 g) N,N-Diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropyl-
amine (LXXXVIII), hydrochloride

From the amine (XLI) of Example 5d). Crude yield 90%. HCl-salt, m.p. 217° (ethanol).

$C_{22}H_{31}NO \cdot HCl \cdot 1/4 H_2O$ (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

15 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).

20 $C_{23}H_{33}NO_2 \cdot HCl$ (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).

25 $C_{22}H_{31}NO_2 \cdot HCl$ (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-phenylpropyl-
amine (XCI), hydrochloride

30 From the amine (LXVIII) of Example 7d). Crude yield 100%. HCl-salt, m.p. 240° (ethanol).

$C_{21}H_{29}NO \cdot HCl$ (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

35 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

- 5 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

- 10 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).

15 $C_{23}H_{33}NO_2.HCl$ (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).

20 $C_{20}H_{25}NO_2.HBr$ (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
 25 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 7i). Crude yield 87%, m.p. 260°. The HCl-salt did not give a satisfactory elemental analysis because of
 30 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
 35 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°.

5 $C_{21}H_{29}NO_2 \cdot HCl \cdot 1/4 H_2O$ (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

10 From the amine (LXXIV) of Example 7j). Crude yield 90%. HCl-salt, m.p. >270° (methanol-water).

$C_{20}H_{27}NO_2 \cdot HCl$ (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

15 From the amine (XLIV) of Example 5g). Crude yield 100%. HCl-salt, m.p. 253° (methanol-ether).

$C_{23}H_{33}NO_2 \cdot HCl$ (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

20 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).

25 $C_{22}H_{31}NO_2 \cdot HCl$ (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).

30 $C_{21}H_{29}NO_2 \cdot HCl$ (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

35 From the amine (LXXVII) of Example 7m). Crude yield 100%, a white powder. HCl-salt, m.p. 209-210°, slow heating, (methanol-acetone).

$C_{20}H_{27}NO_2 \cdot HCl \cdot 1/4 H_2O$ (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

5 From the amine (LXXVIII) of Example 7n). Crude yield 100%. HCl-salt, m.p. 255° (acetone-ether).

$C_{20}H_{27}NO \cdot HCl$ (333.9) requires: C 71.94 H 8.45 N 4.20 Cl 10.62
 Found 71.9 8.43 4.01 10.5

10 y) N-Methyl-N-tert.butyl-3-(2,6-dihydroxyphenyl)-3-phenylpropyl-
 amine (CV), hydrochloride

From the amine (LXXXI) of Example 8c) with BBr_3 , in low yield. HCl-salt, m.p. 170° (ethanol-ether).

$C_{20}H_{27}NO_2 \cdot HCl \cdot 1/2 H_2O$ (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

15 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°.

25 $C_{21}H_{28}ClNO \cdot HCl$ (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-phenyl-
 propylamine

30 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
 35 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-tetramethyl-pyrrolidine

5 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

10 ac) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-4-hydroxy-2,2,6,6-tetramethylpiperidine

15 The benzyloxy compound from Example 5o) was hydrogenolysed as described in Example 9q). The free base was converted to the hydrochloride semihydrate which was crystallized from acetone. The compound melts with decomposition at about 150°C.

$C_{24}H_{33}NO_2.HCl. 1/2 H_2O$ (413.0) requires: C 69.79 H 8.54 N 3.39 O 9.68 Cl 8.58
 Found: 70.0 8.67 3.47 9.98 8.13

ad) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

20 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.

25 $C_{20}H_{27}NO_2.HCl$ (349.9) requires: C 68.65 H 8.06 N 4.00 O 9.15 Cl 10.13
 Found: 68.25 8.18 3.98 9.12 10.0

ae) N-1-Adamantyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

30 The benzyloxy compound from Example 7q) was hydrogenolysed as described in Example 9q). The free hydroxyamine was obtained as a glassy mass. It was dissolved in anhydrous ether and treated with an excess of hydrogen chloride in ether. The hydrochloride precipitated as a powder which decomposed at about 220°C.

$C_{26}H_{33}NO.HCl$ (412.0) requires: C 75.79 H 8.32 N 3.40 O 3.88 Cl 8.61
 Found: 75.3 8.01 3.22 3.45 8.96

Example 10Reduction 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)
5 (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
10 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
15 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
25 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
30 similarly prepared. The hydrochloride melts at 202-3°C.

Example 12Separation 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
35 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 $(\alpha)_D^{20} -10.6^\circ$ (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, $(\alpha)_D^{20} -5.4^\circ$ (c = 5% in methanol).

(+)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared using D-(-)-tartaric acid. The hydrogen-D-(-)tartrate has $(\alpha)_D^{20} +10.0^\circ$. The free amine has $(\alpha)_D^{20} +5.6^\circ$, 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 NaHCO₃ 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°.

C₁₇H₁₆O₃ (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).

C₁₆H₁₃O₃ (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 quantitative 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-toluene-sulphonate (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).

$\text{C}_{25}\text{H}_{28}\text{O}_5\text{S}$ (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-toluene-sulphonate (CXIII) was obtained in the same way in quantitative yield from the propanol CX of Example 15m. M.p. 97-98° (acetone/IPE).

$\text{C}_{24}\text{H}_{25}\text{ClO}_5\text{S}$ (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 (elution 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°.

$C_{21}H_{29}ClNO_2 \cdot HCl$ (398.38) requires: C 63.3 H 7.34 N 3.52 Cl 17.80
 Found: 63.2 7.46 3.49 17.4

q) N-tert.Butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXVIII) was obtained in a similar way in 89% crude yield from the tosylate CXII of Example 16n). The HCl-salt had m.p. 225°.

$C_{22}H_{31}O_2N \cdot HCl$ (377.97)

Requires: C 69.91 H 8.54 N 3.71 Cl 9.38 O 8.47
 Found: 69.8 8.73 3.60 9.45 8.79

Example 19 (continuation of Example 7)

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

r) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIX) was prepared in 89% yield from the amine CXVII of Example 18p) in the manner described for the amine LXI of Example 7a). The HCl-salt was prepared by treating an acetic solution of the free base with concentrated 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)

5 The amine CXV from Example 17s) (26.5 g, 0.072 mol) in methanol was treated with a slight excess of concentrated hydrochloric acid. The mixture was taken to dryness in vacuum, pyridinium chloride (25.4 g, 0.22 mol) was added and the mixture was then heated at 200-205° for 1 ½ h. The mixture was cooled to about 80°, acetone (20 g) was added
10 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)

15 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).

20 $C_{21}H_{28}NO_2 \cdot HCl$ (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
25 from the amine CXX of Example 19s). The HCl-salt had m.p. 240° (acetone).

$C_{21}H_{29}NO_2 \cdot HCl$ (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
30 from the amine CXIX of Example 19r). M.p. >250°.

$C_{20}H_{26}ClNO_2 \cdot HCl$ (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-tetra-methylpyrrolidine (CXXV) was obtained when the O-benzylated amine CXVI of Example 17t) was hydrogenolyzed as described in Example 9q. The hydrochloride melts at 240°.

5 C₂₄H₃₄ClNO (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-phenylpropionamide

10 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamide was obtained as a 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,
 15 0,17 mol) diluted with an equal weight of toluene. The mixture was stirred at 60-70° for 2 h, cooled, treated with excess of 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
 20 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°.

C₂₂H₃₁ON.C₄H₄O₄ (441.58) requires: C 70.72 H 7.99 N 3.17 O 18.12
 Found: 70.7 7.96 3.13 18.0

25

Example 22

Separation of (+)- and (-)-enantiomers

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen tartrate

30 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 $[\alpha]_{D}^{25} +29.5^{\circ}$ (C 5%, methanol) was 34,3 g. Two recrystallisa-
 35 tions from ethanol afforded 21.8 g with $[\alpha]_{D}^{25} +36.0^{\circ}$.

$C_{26}H_{37}NO_7$ requires:	C 65.66	H 7.84	N 2.95	O 23.55
Found:	65.9	8.06	2.90	23.5

5 (-)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine
hydrogen D(-)-tartrate was similarly prepared using D(-)-tartaric acid.
 $[\alpha]_{D}^{25}$ -35.8° .

Found: C 65.6 H 8.00 N 2.83 O 23.6

10 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
15 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

20 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
25 3-5 mm long were prepared by cutting in a parallel direction to the longitudinal
muscle fibres, on each half of the bladder.

30 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, $37^\circ C$, 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 isometric tension of the preparations was recorded by a Grass
polygraph model 79D. The resting tension was applied to approximately 5 mN.
35 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 (carbamylocholin chloride) were studied, in order to determine a suitable agonist concentration for inhibition studies with antagonist. The carbachol concentration chosen, $3 \times 10^{-6} \text{M}$, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol ($3 \times 10^{-6} \text{M}$) 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 $3 \times 10^{-6} \text{M}$ 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 $3 \times 10^{-7} \text{M}$

The chosen doses give about 70% of maximal response. The agonist is

added to the bath at 10-minute 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 measured. 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

15 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% O₂ + 6.5% CO₂)

20 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-minute 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.

35 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.

LD₅₀-interval: The LD₅₀-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 anaesthetized 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 1

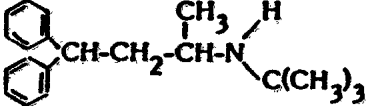
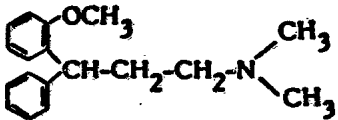
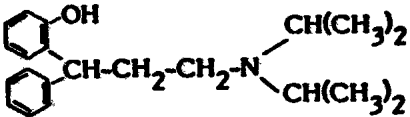
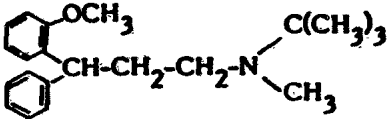
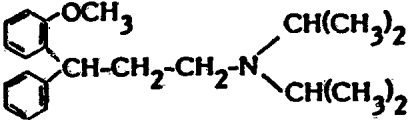
Substance	Antichol. effect IC ₅₀ (M)	Anti-N.A. effect IC ₅₀ (M)	Anti-Ca effect IC ₅₀ (M)	Anti-HI effect IC ₅₀ (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
 Terodiline (prior art)	5.2×10^{-7}	2.4×10^{-6}	10^{-5}	4×10^{-6}	15-20	20	1-3
 GB-A-1.169.944 (antidepressant)	1.2×10^{-6}	4.4×10^{-6}	2.1×10^{-5}	3.7×10^{-7}	10-15	15	
 1 Racemate	1.8×10^{-8}	10^{-5}	1.5×10^{-5}	7×10^{-6}	10-20	20	1-3
1a (+)-isomer of 1	1.8×10^{-8}						
1b (-)-isomer of 1	1.4×10^{-8}						
 2	1.5×10^{-7}	3.5×10^{-6}	9×10^{-6}		10-20	20	
 3	2.4×10^{-7}	3.6×10^{-6}	$>10^{-4}$		3-10	10	

Table I (cont.)

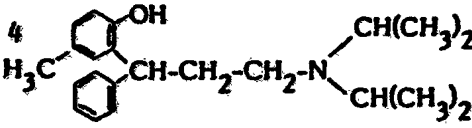
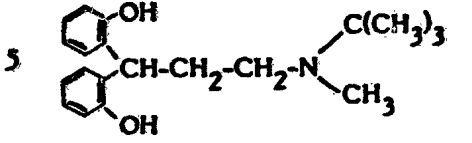
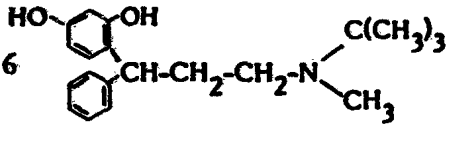
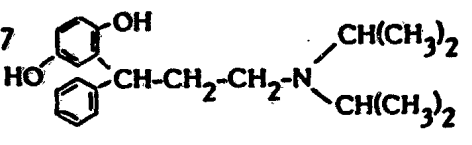
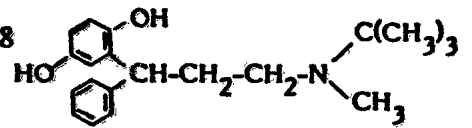
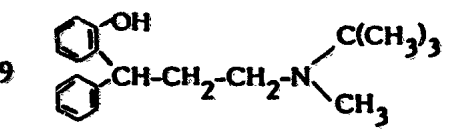
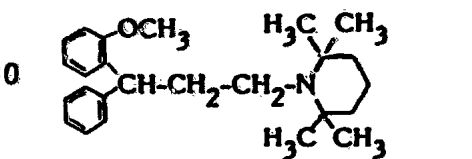
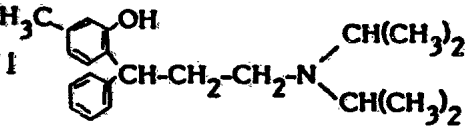
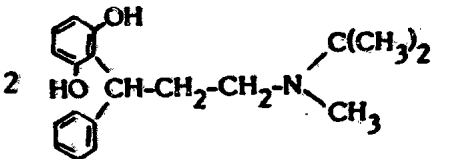
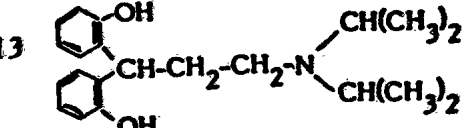
Substance	Antichol. effect IC ₅₀ (M)	Anti-N.A. effect IC ₅₀ (M)	Anti-Ca effect IC ₅₀ (M)	Anti-HI effect IC ₅₀ (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
4 	1.5x10 ⁻⁸	5.5x10 ⁻⁶	6x10 ⁻⁶	10 ⁻⁵	30-40	40	
4a. (+)-isomer of 4 tartrate	1.3x10 ⁻⁸		6.5x10 ⁻⁶		10-20	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-HI effect IC ₅₀ (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
8 	3.1x10 ⁻⁸	5x10 ⁻⁵	>5x10 ⁻⁵	7x10 ⁻⁶	> 6	>6	
9 	1.6x10 ⁻⁸	5x10 ⁻⁵	2.5x10 ⁻⁵	1.2x10 ⁻⁶		20	
10 	6.2x10 ⁻⁸	4x10 ⁻⁶	7x10 ⁻⁶	2.5x10 ⁻⁶			
11 	1.0x10 ⁻⁸	5.5x10 ⁻⁶	10 ⁻⁵	2.5x10 ⁻⁶	10-20	20	
12 	4.7x10 ⁻⁷		2.3x10 ⁻⁵	8.0x10 ⁻⁶	15-30	30	
13 	9.0x10 ⁻⁹	3x10 ⁻⁵	1.5x10 ⁻⁵	2x10 ⁻⁵	5-10	10	

Example APreparation of tablets

	<u>Ingredients</u>	<u>mg/tablet</u>
	1. Compound 1 in Table 1	2.0
5	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	<u>0.75</u>
10		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.

15

Example BPreparation of capsules

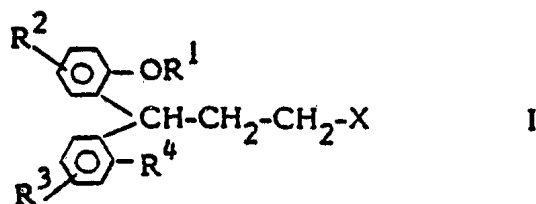
	<u>Ingredients</u>	<u>mg/capsule</u>
	1. Compound 1 in Table 1	2
	2. Lactose	186
20	3. Corn starch	20
	4. Talc	15
	5. Magnesium stearate	<u>2</u>
		225 mg

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.

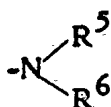
25

CLAIMS

1. 3,3-Diphenylpropylamines of formula I



- 5 wherein R¹ signifies hydrogen or methyl, R², R³ and R⁴ independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II



- 10 wherein R⁵ and R⁶ ^{may carry one or more hydroxy groups and/or} signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R⁵ and R⁶ 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.

- 15 2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R⁵ and R⁶ independently signifies a saturated hydrocarbyl group, especially saturated alifatic hydrocarbyl groups such as C₁₋₈-alkyl, especially C₁₋₆-alkyl, or adamantyl, R⁵ and R⁶ together comprising at least three, preferably at least four carbon atoms.

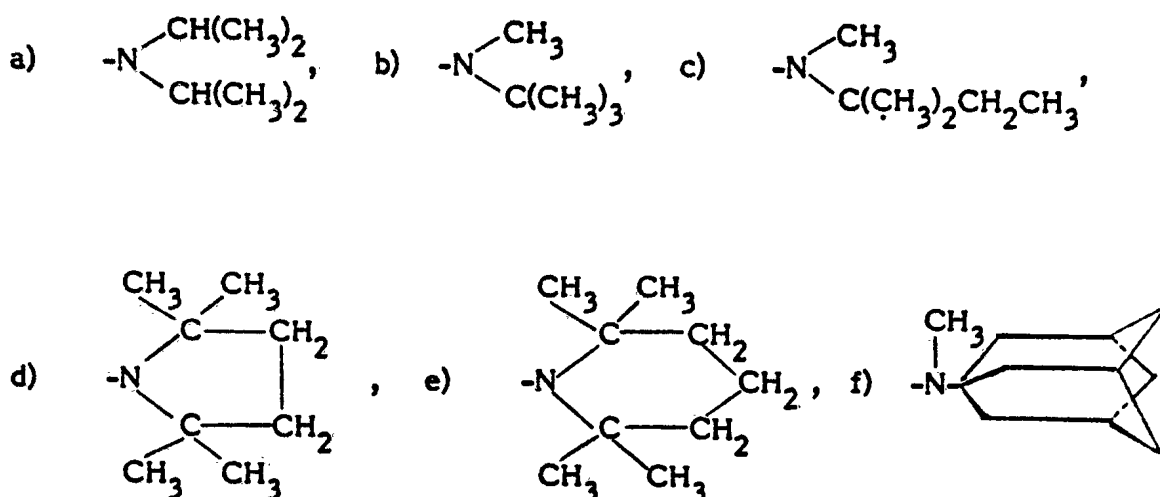
- 20 3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein R⁵ and R⁶ taken together form a ring with the amine nitrogen.

4. 3,3-Diphenylpropylamines according to claim 1, 2 or 3, wherein R⁵ and/or R⁶ carries at least one hydroxy substituent.

5. 3,3-Diphenylpropylamines according to any one of the preceding claims, wherein at least one of R⁵ and R⁶ comprises a branched carbon chain.

- 25 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:





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:

- 5 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,
 10 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,
 15 ~~(+)-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.

20 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~~



11. **N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine, its salt with physiologically acceptable acids and its racemates and individual enantiomers.**

12. **3,3-Diphenylpropylamines as claimed in any one of claims 1-7 and 11, wherein the compound is the (+)-isomer.**

13. **(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl-propylamine, its salt with physiologically acceptable acids and its racemates and individual enantiomers.**

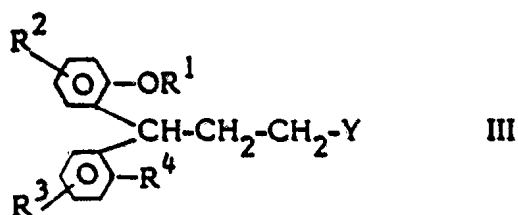
14. **3,3-Diphenylpropylamines according to any one of claims 11, 12 and 13 for use as pharmaceutically active substances, especially as anticholinergic agents.**

15. **A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 11, 12 and 13 and a compatible pharmaceutical carrier.**

16. **Use of a 3,3-diphenylpropylamine according to any one of claims 11, 12 and 13 for preparing an anticholinergic drug.**

17. **A method for preparing 3,3-diphenylpropylamines according to any one of claims 1-7, 11, 12 and 13, comprising:**
 - a) **reacting a reactively esterified 3,3-diphenylpropanol of formula III**



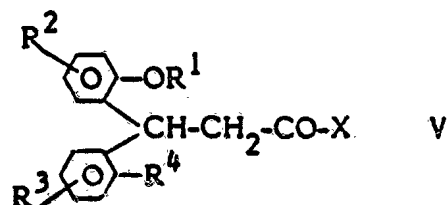


wherein R^1 - R^4 are as defined above, any hydroxy groups may be protected and Y is a leaving group,
with an amine of formula IV



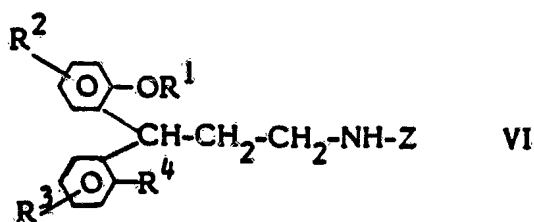
wherein X is as defined above, or

b) reducing a 3,3-diphenylpropionamide of formula V



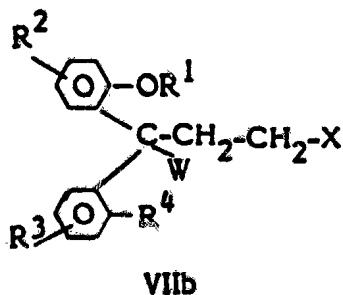
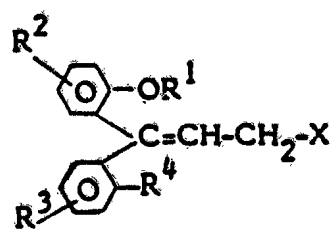
wherein R^1 - R^4 and X are as defined above and any hydroxy groups may be protected, or

10 c) N-methylating a secondary 3,3-diphenylpropylamine 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

15 d) reducing a 3,3-diphenylpropylamine of formula VIIa or 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

- 5 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
- 10 iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

INTERNATIONAL SEARCH REPORT.

International Application No PCT/SE89/00016

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
C 07 C 91/28, 93/14, A 61 K 31/135		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC 4	C 07 C 91/28, 91/30, 93/14; A 61 K 31/135	
US C1	260:568, 570.5, 571, 573; 564:316; 424:330; 514:648, 654	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	SE,A, 215 499 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 26 September 1976	1-11
X	DK,A, 111 894 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) 21 October 1968 see page 1- page 2, line 9; the claim	1-11
X	US,A, 3 446 901 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 27 May 1969 see column 1, line 29 - line 55 & GB, 1169945	1-2, 7-11
X	GB,A, 1 169 945 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2 & US, 3446901	1-2, 7-11
.../...		
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"Δ" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1989-03-30	1989 -04- 05	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	Irja Berlin <i>Irja Berlin</i>	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE /partly unsearchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers... because they relate to subject matter not required to be searched by this Authority, namely:
2. Claim numbers... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
 The expression "R⁵ and R⁶ may form a ring together with the amine nitrogen" (claims 1, 3, 4 and 8-11) is indefinite.
 The search on claims 1, 3, 4 and 8-11 has therefore been incomplete.
3. Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	GB, A, 1 169 944 (ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 5 November 1969 see the claims 1-2	1-2, 7-11
X	Chemical Abstracts Vol. 97 (1982) abstract 120105n, Biol. Zh. Arm. 1982, 35(2), 101-7 (Russ).	1,3, 8-10