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(54) **STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**

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(52) **U.S. Cl.** **514/530**; 514/531; 514/534; 514/548; 514/551; 560/61; 560/122; 560/123; 560/124; 560/138; 560/142; 560/250; 564/319

(58) **Field of Search** 514/530, 531, 514/534, 548, 551; 560/61, 122, 123, 124, 138, 142, 250, 37, 18, 42, 140; 564/319

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,686,464 A 11/1997 Johansson et al. 514/315

FOREIGN PATENT DOCUMENTS

DE	693 17 898 T2	10/1998	..... C07C/217/62
EP	0 667 852 B1	4/1998	..... C07C/217/62
EP	0 957 073 A1	11/1999	..... C07C/1/00
WO	9411337	5/1994	
WO	9843942	10/1998	
WO	9958478	11/1999	

OTHER PUBLICATIONS

Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU–200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology. vol. 81, pp. 169–172 (1997).*

L. Palmer, L. Andersson, T. Andersson, U. Stenberg: *Determination of tolterodine and the 5–hydroxymethly metabolite in plasma, serum and urine using gas chromatography–mass spectrometry; Journal of Pharmaceutical and Biomedical Analysis*; Jan. 20, 1997; pp. 155–165.

* cited by examiner

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(57) **ABSTRACT**

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

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

24 Claims, 1 Drawing Sheet

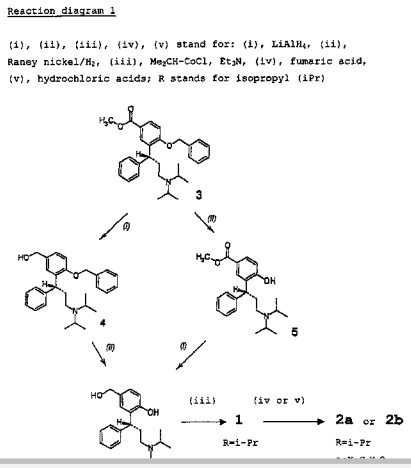
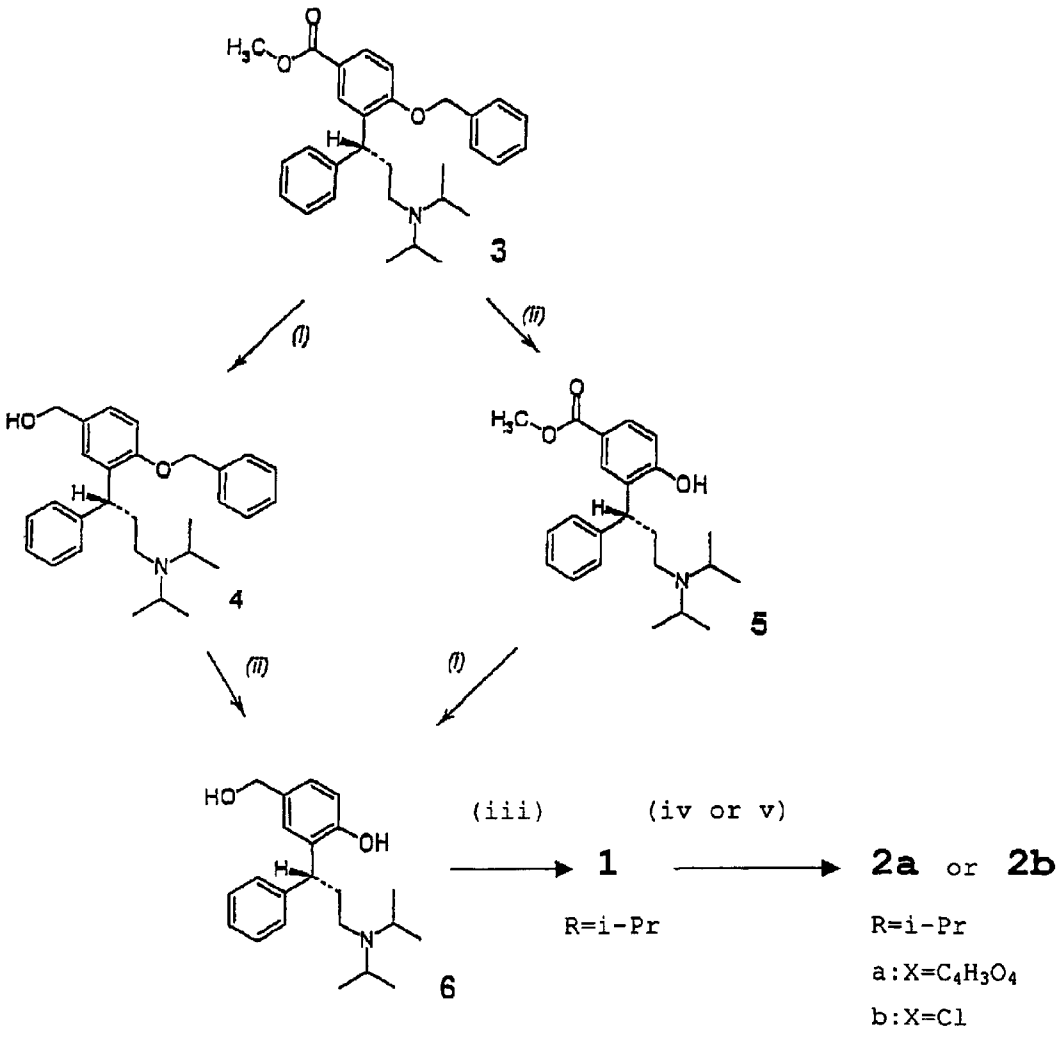


Figure 1

Reaction diagram 1

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



STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

This application was filed under 35 U.S.C. 371, and is the U.S. National Stage of PCT/EP00/11309, filed 5 Nov. 2000.

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

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

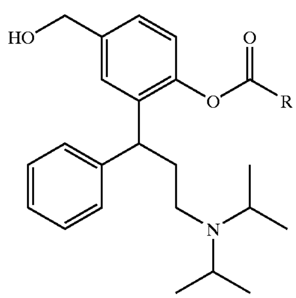
From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

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

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

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

Formula A



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

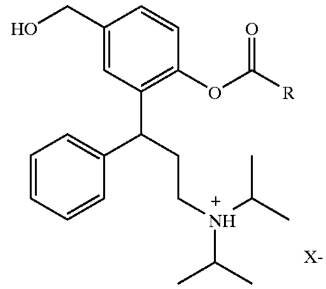
Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification. During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

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

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been pre- general formula H-X, in which $^-$X represents the respective acid residue, into their respective salt with general formula I.

Formula I



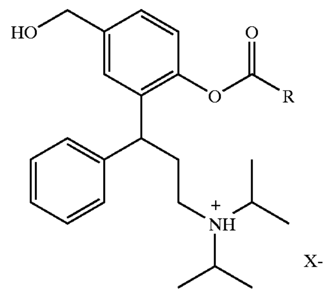
The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed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

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

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

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

Formula I



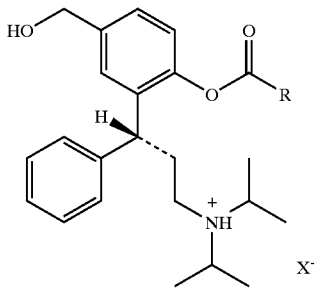
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

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

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-

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

Formula 2



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

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

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

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

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

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

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

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

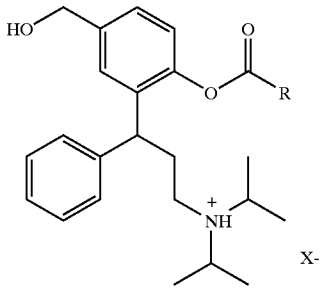
The expression "phenyl" designates a —C_6H_5-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable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

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

The method is characterised by chemo- and regioselectivity.

Compounds of General Formula I

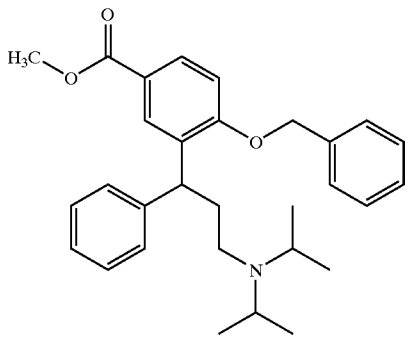
Formula I



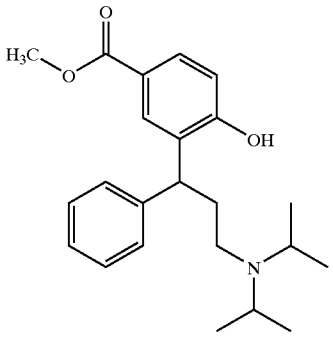
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are that

a) a compound of formula III

Formula III



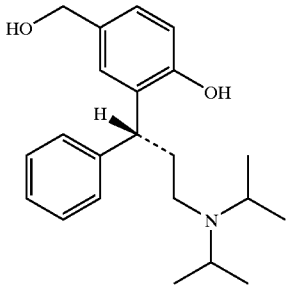
Formula V



whereupon

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

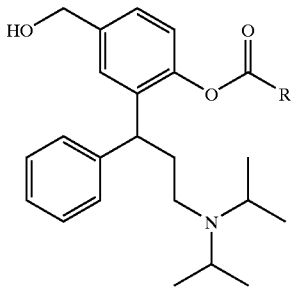
Formula VI



which

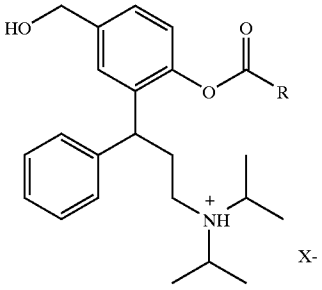
c) is converted with an acylation agent, in order to obtain of formula A

Formula A



in which R has the significance stated above, which d) is

Formula I

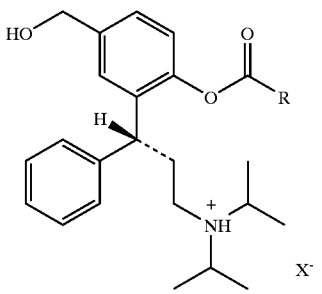


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

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

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

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of

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