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PATENT SPECIFICATION

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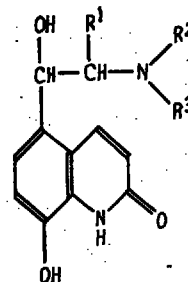
(54) 5-SUBSTITUTED-ALKYL-8-HYDROXYCARBOSTYRIL DERIVATIVES AND PRODUCTION THEREOF

(71) We, OTSUKA PHARMACEUTICAL CO., LTD., a Japanese Company, of No. 9, Kanda Tsukasa-Cho 2-Chome, Chiyoda-Ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 5 - (substituted) - alkyl - 8 - hydroxycarbostyryl derivatives, to acid addition salts thereof and to a process for preparing them.

It is well known that certain carbostyryl derivatives exhibit useful pharmaceutical activities. Representative compounds of this type have been disclosed in *Journal of Medical Chemistry*, Vol. 15, No. 3, pp. 260 266 (1972), Japanese Patent Publication No. 38789/1971 and *Chemical Abstracts*, 62, 16212e (1965), etc.

According to the present invention there are provided 5 - [(1 - hydroxy - 2 - substituted - amino)alkyl - 8 - hydroxycarbostyryl derivatives represented by the following general formula (I):

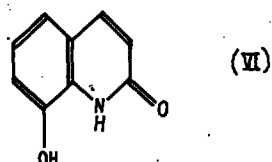


wherein R¹ represents an alkyl group having 1 to 4 carbon atoms and R² and R³, which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, an aralkyl group containing a straight or branched chain alkyl moiety having from 1 to 4 carbon atoms or a cycloalkyl group having 4 to 6 carbon atoms, or R² and R³ may, when taken together with the nitrogen atom to which they are attached, form a 5- or 6-membered substituted or unsubstituted heterocyclic ring containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms.

The present invention also provides a

process for preparing the above 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivatives represented by the general formula (I) which comprises the steps of:

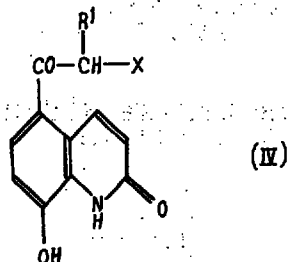
(1) reacting 8 - hydroxycarbostyryl of the following general formula (VI):



with an α - halo - alkanolic acid halide of the following general formula (V):

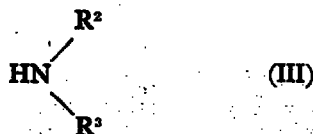


wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X and X' may be the same or different and each represents a halogen atom, in the presence or absence of a solvent and in the presence of a Lewis acid catalyst, to obtain a 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl derivative of the following general formula (IV):

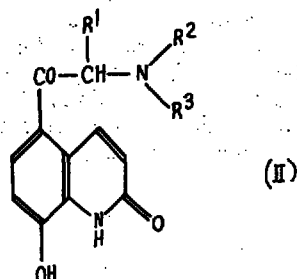


wherein R and X are as defined above,

(2) reacting the 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl thus obtained with ammonia or an amine of the following general formula (III):



wherein R^2 and R^3 are as defined above, in the presence or absence of a solvent, to obtain a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyryl of the following general formula (II):



wherein R^1 , R^2 and R^3 are as defined above, and

(3) reducing the 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyryl of the general formula (II) with hydrogen in the presence of a hydrogenation catalyst or with a reducing agent.

The 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivatives of the general formula (I) and the acid addition salts thereof exhibit a β - adreno-receptor stimulating activity and, therefore, are useful as bronchodilators, peripheral vasodilators or as antihypertensive agents.

The term "alkyl" as used herein means a straight or branched chain alkyl group. Suitable examples of such groups having 1 to 4 carbon atoms include, for example, methyl, ethyl, propyl, *iso* - propyl, butyl, *sec* - butyl and *tert* - butyl groups.

The term "aralkyl" as used herein means an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms, for example, a benzyl, α - methylbenzyl, α,α - dimethylbenzyl, phenethyl or α,α - dimethylphenethyl group.

The term "cycloalkyl" as used herein means a cycloalkyl group having 4 to 6 carbon atoms, for example, a cyclobutyl, cyclopentyl or cyclohexyl group.

The term "5- or 6-membered substituted or unsubstituted heterocyclic ring" as used herein means a heterocyclic group containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms such as a pyrrolidino, pyrrolidinyl, piperidino, piperidinyl, morpholino, morpholinyl, piperazino or piperazinyl group which may be unsubstituted or substituted with an alkyl group having 1 to 4 carbon atoms, such as a methyl, ethyl, *iso* - propyl or *tert* - butyl group, for example, a 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine and the halogen is preferably chlorine or bromine.

The 8 - hydroxycarbostyryl of the formula (VI) used as a starting material of the present invention is a known compound, and may easily be prepared, for example, by the method as described in George R. Pettit et al, *J. Org. Chem.*, 33, 1089 (1968).

The α - halo - alkanolic acid halide of the formula (V) which may be used in this invention includes α - chloropropionyl chloride, α - bromopropionyl chloride, α - chlorobutyryl chloride, α - bromobutyryl chloride, α - bromobutyryl bromide and α - chlorovaleryl chloride.

The reaction between the 8 - hydroxycarbostyryl of the formula (VI) and the α - halo - alkanolic acid halide of the formula (V) can be conducted using a Lewis acid as a catalyst, for example, aluminium

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chloride, aluminium bromide, ferric chloride, stannic chloride, titanium chloride or boron trifluoride, with aluminium chloride being preferred. The Lewis acid may be used in an amount of from 2 to 10 moles, preferably from 3 to 6 moles per mole of the 8 - hydroxycarbostyryl of the formula (VI). The α - halo - alkanolic acid halide of the formula (V) is generally used in from an equimolar amount to a large excess relative to the 8 - hydroxycarbostyryl of the formula (VI) and preferably in an amount of 2 to 20 moles, preferably 2 to 10 moles, per mole of the 8 - hydroxycarbostyryl of the formula (VI). The reaction can be carried out in the absence or presence of an appropriate solvent such as carbon disulphide or nitrobenzene, preferably carbon disulphide, in a volume of from 0.5 to 20, preferably from 2 to 10 times the volume of the reactants, and in the presence of the above enumerated catalyst under anhydrous conditions at the room temperature (20 to 30°C) to 150°C, preferably from room temperature to 80°C, for a period of from 1 to 20, preferably from 1 to 10, hours.

The amines of the formula (III) which can be used in the reaction with 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl of the formula (IV) include alkylamines, for example, methylamine, ethylamine, *n* - propylamine, *iso* - propylamine, *n* - butylamine, *sec* - butylamine and *tert* - butylamine; cycloalkylamines, for example, cyclobutylamine, cyclopentylamine and cyclohexylamine; aralkylamines, for example, benzylamine, α - methylbenzylamine, α,α - dimethylbenzylamine, phenethylamine and α,α - dimethylphenethylamine and substituted or unsubstituted heterocyclic amines, for example, pyrrolidine, piperidine, morpholine, piperazine, 2 - methylpiperidine, 3 - methylpiperidine and *N* - methylpiperazine.

This reaction between the amine of the formula (III) and the 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl of the formula (IV) can be effected using the amine of the formula (IV) in from an equimolar amount to a large excess, preferably from 2 to 10 moles per mole of the compound of the formula (IV), at a temperature of from room temperature to the refluxing temperature of the reaction system, preferably at a temperature of from 40° to 100°C at from atmospheric pressure to 10 atmospheres in an appropriate solvent or using the amine of the formula (III) *per se* as a solvent. Suitable solvents which can be used in this reaction include lower alcohols such as methanol, ethanol and propanols and ethers such as dioxane and diethyl ether, esters such as ethyl acetate, aromatic hydrocarbons such as benzene, toluene and xylene and nitrile

solvents such as acetonitrile. Ethanol and isopropanol are preferred.

The subsequent reduction of the thus-obtained 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyryl of the formula (II) can be conducted using a reducing agent such as lithium aluminium hydride or sodium borohydride, or by catalytic reduction with hydrogen in the presence of a hydrogenation catalyst such as palladium black, palladium-on-carbon, Raney nickel, platinum black or platinum oxide.

The reducing agent may be used in an amount of from 2 to 10 moles, preferably from 2 to 5 moles, per mole of the carbostyryl compound of the formula (II) in a solvent while cooling under atmospheric pressure at a temperature of from 0 to 100°C, preferably from 20 to 50°C. When sodium borohydride is used as the reducing agent, the solvent is preferably water or alcohols such as methanol or ethanol, and when lithium aluminium hydride is used as the reducing agent, the solvent is preferably a non-aqueous solvent such as anhydrous diethyl ether, ethyl acetate or tetrahydrofuran.

The catalytic reduction may be carried out with hydrogen using a hydrogenation catalyst in an amount of from 0.05 to 1 mole, preferably from 0.1 to 0.5 mole, per mole of the carbostyryl compound of the formula (II) in a solvent, for example, water or an alcohol such as methanol, ethanol or *iso* - propanol under a hydrogen atmosphere at a pressure of from atmospheric pressure to 100 atmospheres, preferably from atmospheric pressure to 50 atmospheres, at a temperature of from room temperature to 150°C, preferably from room temperature to 120°C, advantageously with agitation of the reduction system. It is advantageous to carry out the above catalytic reduction at a temperature higher than 50°C at atmospheric pressure or at a temperature higher than room temperature under pressure.

The compounds of the present invention represented by the formula (I) wherein R^2 and R^3 represent hydrogen atoms can also be prepared from the compounds of the formula (II) wherein either R^2 or R^3 represents a benzyl group or an α - methylbenzyl group. The above benzyl or α - methylbenzyl group can easily be split off during the catalytic reduction to produce compounds of the general formula (I) wherein R^2 and R^3 are hydrogen atoms.

Alternatively, a carbostyryl derivative represented by the general formula (I) may be prepared from a corresponding 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyryl of the following general formula (VII):

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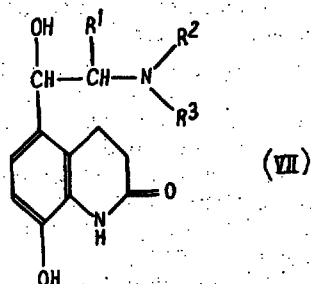
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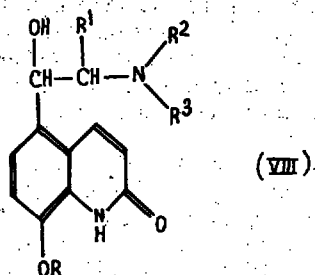


wherein R^1 , R^2 and R^3 are as hereinbefore defined, by dehydrogenation.

The compounds of general formula (VII) and a process for their preparation are described and claimed in our copending Patent Application No. 55898/74 (Serial No. 1,496,767) of even date.

The dehydrogenation can be carried out by any suitable procedure useful for liberating a hydrogen atom from the 3- and the 4-positions of the carbostyryl moiety, for example, by (1) a procedure using a dehydrogenation agent such as chloranil(tetrachloro-1,4-benzoquinone) or dichlorodicyano-1,4-benzoquinone, (2) a procedure using a metal catalyst for dehydrogenation such as palladium black, platinum black, platinum oxide or Raney nickel, or (3) a procedure using selenium dioxide or sulphur. However, for ease of operations, the procedure (1) or (2) above is conveniently used in the present invention.

Further, carbostyryl derivatives represented by the general formula (I) may be prepared by dealkylating a 5-[1-hydroxy-2-(substituted-amino)alkyl]-8-alkoxycarbostyryl derivative of the following general formula (VIII):



wherein R , R^1 , R^2 and R^3 are as hereinbefore defined, with a hydrohalic acid. Compounds of the general formula (VIII) and a process for their preparation are described and claimed in our copending Patent Application No. 55929/74 (Serial No. 1,496,770) of even date.

The compounds of formula II from the subject of our copending Patent Application No. 28863/77 (Serial No. 1,496,874) of even date.

The dehydrogenation is generally carried out in a solvent, for example, aromatic hydrocarbons such as benzene, toluene,

xylene, phenetol and chlorobenzene, lower alcohols such as methanol, ethanol, *iso*-propanol or *tert*-butanol, ethers such as dioxane, ketones such as acetone or in water or acetic acid, in the presence of a dehydrogenation agent or dehydrogenation metal catalyst as enumerated above, at a temperature of from room temperature to the refluxing temperature of the dehydrogenation reaction system, preferably at the refluxing temperature, for a period of from 10 to 30 hours. The dehydrogenation agent is generally used in an amount of from 1 to 5 moles per mole of the 3,4-dihydrocarbostyryl of the general formula (VII), and the metal catalyst is generally used in an amount of 0.5 to 3 moles per mole of the 3,4-dihydrocarbostyryl of the general formula (VII).

The 5-[1-hydroxy-2-(substituted-amino)alkyl]-8-hydroxycarbostyryl derivatives of the general formula (I) as obtained above are basic substances and can form acid addition salts with various organic or inorganic acids. Particularly useful examples of such salts are the pharmaceutically acceptable acid addition salts formed with inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid and hydrobromic acid, or organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid and ascorbic acid. These acid addition salts can easily be prepared by well known procedures, for example, by adding from an equimolar to an excess amount of the acid to a solution of the compound of the general formula (I) dissolved in an appropriate organic solvent such as methanol, ethanol, *iso*-propanol or acetone.

Both the free bases of the compounds of the formula (I) and the acid addition salts thereof are novel compounds and exhibit a stimulating activity on β -adreno-receptor, and therefore, are very useful as pharmaceuticals such as a bronchodilator, a peripheral vasodilator, an antihypertensive agent and the like, particularly for treating bronchial asthma. As is apparent to one skilled in the art, the compounds of the general formula (I) contain two asymmetrical centres and, therefore, can be present in four optically active forms.

Particularly preferred examples of the compounds of the general formula (I) are the following basic compounds and their hydrochlorides, sulphates, phosphates, maleates, fumarates and oxalates.

- 5 - (1-Hydroxy-2-*iso*-propylamino)-butyl-8-hydroxycarbostyryl;
- 5 - (1-Hydroxy-2-*sec*-butylamino)-butyl-8-hydroxycarbostyryl;
- 5 - (1-Hydroxy-2-*iso*-propylamino)-propyl-8-hydroxycarbostyryl;

- 5 - (1 - Hydroxy - 2 - tert - butylamino) - propyl - 8 - hydroxycarbo-
styryl;
5 - (1 - Hydroxy - 2 - ethylamino)butyl -
8 - hydroxycarbo-
5 5 - [1 - Hydroxy - 2 - (2 - phenethyl-
amino)]butyl - 8 - hydroxycarbo-
styryl.

The present invention will now be further illustrated in greater detail by reference to the following Examples. Unless otherwise indicated, all parts, percentages and ratios are by weight.

EXAMPLE 1

50 Grams of α - bromobutyric acid bromide (V), 50 g of anhydrous aluminium chloride and 400 ml of carbon disulphide were added to 20 g of 8 - hydroxycarbo-
15 styryl (VI). The resulting mixture was heated at a temperature of 50°C for 13 hours and the carbon disulphide layer was removed by decantation. Crushed ice was added to the re-
20 sistance to crystallize the product, and the crystals thus formed were filtered off, washed with water and then recrystallized from methanol to obtain 27 g of 5 - (α - bromo-
25 butyryl) - 8 - hydroxycarbo-
styryl (IV) having a melting point of 218 to 219°C (with colouring and decomposition).

EXAMPLE 2

25 Grams of α - bromobutyric acid chloride (V) and 25 g of anhydrous aluminium chloride were added to 10 g of 8 - hydroxy-
30 carbo-
styryl (VI), and the resulting mixture was heated at a temperature of 70°C for 4 hours while thoroughly stirring. After
35 crushed ice was added to the mixture to crystallize the product, the crystals thus formed were filtered off, washed with water and then recrystallized from methanol to obtain 12.6 g of 5 - (α - bromobutyryl) -
40 8 - hydroxycarbo-
styryl (IV) having a melting point of 218 to 219°C (with colouring and decomposition).

EXAMPLE 3

25 Grams of α - bromobutyric acid bromide (V) and 100 ml of nitrobenzene were added to 10 g of 8 - hydroxycarbo-
45 styryl (VI), and 25 g of anhydrous aluminium chloride were added to the resulting solution under cooling. The mixture was heated at a temperature of 70°C for 10 hours fol-
50 lowed by pouring onto crushed ice. The pre-
cipitated crystals were filtered off, washed with water and recrystallized from methanol to obtain 11.2 g of 5 - (α - bromobutyryl) -
55 8 - hydroxycarbo-
styryl (IV) having a melting point of 217 to 218.5°C (with colouring and decomposition).

EXAMPLE 4

200 Millilitres of *sec* - butylamine (III) were added to 10 g of 5 - (α - bromo-

butyryl) - 8 - hydroxycarbo-
styryl (IV) ob-
tained as described in Examples 1 to 3, and the resulting mixture was heated at a tem-
perature of 60°C for 20 hours followed by evaporation to dryness. Crystals which
65 formed upon addition of water were filtered off, dissolved in 50 ml of ethanol, and the resulting solution was adjusted to a pH of 1 with concentrated hydrochloric acid. The
70 precipitated crystals were filtered off and re-crystallized from methanol to obtain 8.3 g of 5 - (α - *sec* - butylaminobutyryl) - 8 -
hydroxycarbo-
styryl (II) hydrochloride having a melting point of 212 to 214°C (with
75 colouring and decomposition).

EXAMPLE 5

10 Millilitres of *iso* - propylamine (III) and 50 ml of methanol were added to 5 g of the 5 - (α - bromobutyryl) - 8 - hydroxy-
80 carbo-
styryl (IV) obtained in Examples 1 to 3. The resulting mixture was heated under re-
fluxing for 6 hours followed by evaporation to dryness. The reaction product was further worked up in the same manner as described in Example 1 to obtain 4.2 g of a methanol
85 solvate of 5 - (α - *iso* - propylaminobutyryl) - 8 - hydroxycarbo-
styryl (II) having a melting point of 136 to 137°C (with foaming and de-
composition).

EXAMPLE 6

50 Grams of α - bromobutyric acid bromide (V), 50 g of anhydrous aluminium chloride and 400 ml of carbon disulphide were added to 20 g of 8 - hydroxycarbo-
90 styryl (VI). The resulting mixture was heated at a temperature of 50°C for 13 hours and the carbon disulphide layer was removed by decantation. Crushed ice was added to the residue, and the precipitate crystals were
95 filtered, washed with water and recrystallized from methanol to obtain 27 g of 5 - (α - bromobutyryl) - 8 - hydroxycarbo-
styryl (VI) having a melting point of 218 to 219°C (with colouring and decomposition). To 5 g of the thus-obtained 5 - (α - bromobutyryl) -
100 8 - hydroxycarbo-
styryl (IV) were added 100 ml of *iso* - propylamine (III), and the mix-
ture was heated at a temperature of 50°C for 4 hours followed by evaporation to dry-
105 ness. Crystals which formed upon addition of water were filtered off, washed with water and then recrystallized from methanol to obtain 4.6 g of a methanol solvate of 5 -
(α - *iso* - propylaminobutyryl) - 8 - hydroxy-
110 carbo-
styryl (II) having a melting point of 136 to 137°C (with foaming and decomposi-
115 tion).

EXAMPLE 7

25 Grams of 2 - phenethylamine (III) were added to 5 g of the (α - bromobutyryl) -
120 8 - hydroxycarbo-
styryl (IV) prepared as in Example 1, 2 or 3, and the mixture was

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6
5 stirred at a temperature of 30°C for 8 hours. A mixture of diethyl ether and petroleum ether was added to the reaction mixture and the precipitated material was dissolved in dilute hydrochloric acid to remove any insoluble material. The hydrochloric acid layer was concentrated and the precipitate was filtered off and recrystallized from ethanol to obtain 5.3 g of a material having a melting point of 200 to 201°C (with colouring and decomposition). The identity of the material thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - [α - (2 - phenethylamino)butyryl] - 8 - hydroxycarbostyryl (II) hydrochloride dihydrate.

EXAMPLE 8

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20 5 Millilitres of morpholine (III) were added to 5 g of the 5 - (α - bromobutyryl) - 8 - hydroxycarbostyryl (IV) prepared as in Examples 1 to 3, and the mixture was allowed to react at a temperature of 40°C for 4 hours with stirring. The reaction mixture was then concentrated under reduced pressure, and 100 ml of water were added to the resulting residue. The mixture was stirred and filtered and the filtrate mother liquor was then concentrated under reduced pressure. The residue was dissolved in acetone and the solution was filtered to remove any insoluble material. The filtrate was then concentrated under reduced pressure, adjusted to a pH of 2 to 3 with concentrated hydrochloric acid, and the precipitate which formed upon ice-cooling was recrystallized from ethanol to obtain 2.1 g of white amorphous 5 - (α - morpholinobutyryl) - 8 - hydroxycarbostyryl (II) hydrochloride monohydrate having a melting point of 179 to 182°C (with decomposition). The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 9

45 40 Millilitres of methanol were added to 2 g of the 5 - (α - iso - propylaminobutyryl) - 8 - hydroxycarbostyryl (II) obtained as in Example 5 or 6; 2.5 g of sodium borohydride were added portionwise to the resulting solution while stirring under ice-cooling and the mixture was further stirred at room temperature for an additional hour. Concentrated hydrochloric acid was added to the reaction mixture to adjust the pH to 1, and the mixture was then evaporated to dryness. The precipitates were washed with acetone, dissolved in water, and then adjusted to a pH of 8 with aqueous sodium hydroxide to precipitate crystals. The resulting crystals were collected by filtration and recrystallized from ethanol to obtain 1.8 g of 5 - (1 - hydroxy - 2 - iso - propylamino) - butyl - 8 - hydroxycarbostyryl (I) monohydrate.

rate having a melting point of 141 to 142°C (with colouring and decomposition).

EXAMPLE 10

65 30 Millilitres of methanol were added to 1.5 g of the 5 - (α - sec - butylamino - butyryl) - 8 - hydroxycarbostyryl (II) prepared as in Example 4, and 1.5 g of sodium borohydride were added portionwise to the resulting solution while stirring under ice-cooling. The stirring was further continued at room temperature for an additional hour. The reaction mixture was then adjusted to a pH of 1 with concentrated hydrochloric acid followed by evaporation to dryness. The precipitates were filtered off, washed with acetone, dissolved in water and then adjusted to a pH of 8 with aqueous sodium hydroxide. The precipitated crystals were filtered, washed with water and again dissolved in diluted hydrochloric acid. The resulting solution was concentrated to dryness, and the residue was recrystallized from ethanol to obtain 1.3 g of 5 - (1 - hydroxy - 2 - sec - butylamino) - butyl - 8 - hydroxycarbostyryl (I) hydrochloride monohydrate having a melting point of 182 to 183°C (with foaming and decomposition).

EXAMPLE 11

90 20 Millilitres of tetrahydrofuran were added to 1 g of the 5 - (α - iso - propylaminobutyryl) - 8 - hydroxycarbostyryl (II) hydrochloride obtained as in Example 5 or 6, and the resulting mixture was added dropwise to a suspension of 0.12 g of lithium aluminium hydride in 10 ml of tetrahydrofuran while stirring at room temperature. After completion of the addition, a small amount of water was added to the reaction mixture to decompose any excess lithium aluminium hydride. The reaction mixture was then poured into 50 ml of ice-water and the aqueous layer of the resulting solution was separated and evaporated to dryness. The precipitated crystals were filtered off, washed with acetone and dissolved in water. The solution was adjusted to a pH of 8 with aqueous sodium hydroxide to precipitate crystals which were then filtered and recrystallized from ethanol to obtain 0.8 g of 5 - (1 - hydroxy - 2 - iso - propylamino) - butyl - 8 - hydroxycarbostyryl (I) monohydrate having a melting point of 141 to 142°C (with colouring and decomposition).

EXAMPLE 12

120 1.5 Grams of the free base of the 5 - [α - (2 - phenethylamino)butyryl] - 8 - hydroxycarbostyryl (II) prepared as in Example 7 were dissolved in 150 ml of methanol, and 2 g of sodium borohydride were added slowly to the solution under ice-

water cooling while stirring. Stirring was then continued at room temperature for an additional hour. The resulting mixture was then adjusted to a pH of 1 with concentrated hydrochloric acid and the mixture was filtered to remove the precipitate formed. The filtrate was evaporated to dryness, and the residue was crystallized by adding acetone. An aqueous sodium hydroxide solution was then added to the crystals to a pH of 8. The precipitate formed was filtered and recrystallized from ethanol to obtain 1.3 g of a white amorphous material having a melting point of 147 to 148°C (with foaming and decomposition). The identity of the material thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - [1 - hydroxy - 2 - (2 - phenethylamino)]butyl - 8 - hydroxycarbostryl (I) trihydrate.

EXAMPLE 13

2.5 Grams of chloranil and 20 ml of xylene were added to 2.2 g of 5 - (1 - hydroxy - 2 - iso - propylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostryl (VII), and the mixture was heated under reflux for 24 hours. The reaction mixture was evaporated to dryness and the residue was washed thoroughly with 50 ml of carbon tetrachloride. The residue was then dissolved in 30 ml of methanol and hydrogen chloride gas was introduced into the solution to bring it to a pH of 1, and the solution was then cooled. The precipitated crystals were filtered off and recrystallized from methanol to obtain 1.5 g of a material having a melting point of 164 to 166°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (1 - hydroxy - 2 - iso - propylamino)propyl - 8 - hydroxycarbostryl (I) hydrochloride monohydrate.

In the same manner as described in the above Example 13, the following compounds of the general formula (I) were also prepared from corresponding 3,4 - dihydrocarbostryl compounds of the general formula (VII):

5 - (1 - Hydroxy - 2 - sec - butylamino)-butyl - 8 - hydroxycarbostryl hydrochloride monohydrate having a melting point of 182 to 183°C (with decomposition).

5 - (1 - Hydroxy - 2 - ethylamino)butyl - 8 - hydroxycarbostryl hydrochloride having a melting point of 174 to 177.5°C (with decomposition).

EXAMPLE 14

10 Millilitres of a 47% aqueous hydrobromic acid were added to 1 g of 5 - (1 - hydroxy - 2 - iso - propylamino)propyl - 8 - methoxycarbostryl hydrochloride (VIII) monohydrate; and the mixture was heated under refluxing for 15 hours and then evaporated to dryness. Acetone was added to

the resulting residue to crystallize the product which was then adjusted to a pH of 8 with dilute aqueous sodium hydroxide solution. The precipitated crystals were filtered off, washed with water and dissolved in ethanol. The solution was adjusted to a pH 1 with concentrated hydrochloric acid and evaporated to dryness. The residue thus obtained was recrystallized from a mixture of ethanol and diethyl ether to obtain 0.7 g of a material having a melting point of 164 to 166°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (1 - hydroxy - 2 - iso - propylamino)propyl - 8 - hydroxycarbostryl (I) hydrochloride.

In the same manner as described in Example 14, the following compound of the general formula (I) was obtained from the corresponding 8 - methoxy compound of the general formula (VIII).

5 - (1 - Hydroxy - 2 - iso - propylamino)-butyl - 8 - hydroxycarbostryl hydrochloride having a melting point of 213 to 214°C (with decomposition).

REFERENCE EXAMPLE

The stimulating activity of the compounds of this invention on β - adreno - receptor was determined as follows:

Male hybrid adult dogs, weighing 10 to 15 kg were anaesthetized with 30 mg/kg of body weight of sodium pentobarbital administered intravenously. Each of the anaesthetized dogs was secured on its back and a cannula was inserted into the trachea. Artificial respiration was conducted using a device according to the Konzett-Rössler method (Konzett H. & Rössler R., "Versuchsanordnung zu Untersuchungen und der Bronchial Moskolatur", *Arch. Exp. Path., Pharmacol.*, 195, 71 to 74, 27 to 40 (1940)). The volume of the overflowing air at the time of inhalation was measured through a pneumotachometer to determine the bronchial resistance and the values obtained were recorded on a polygraph.

In the above experiment, histamine was employed as a bronchoconstrictor at a dosage level of 10 mg/kg of body weight, and an aqueous solution containing each of the test compounds and controls shown in Table 1 below was then administered to each of the anaesthetized dogs through the femoral vein at the various dosage levels as shown in Table 1 below 1 minute before the administration of the histamine. Sodium pentobarbital was infused during the experiment at a dosage level of 4 mg/kg of body weight/hr using an automatic injector in order to inhibit spontaneous respiration and to keep the anaesthetic condition constant over the test period. The results obtained are shown in Table 1 below.

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TABLE 1

Bronchial Resistance (%)

Dosage Level (μ /Kg)

Compound	0.01	0.03	0.1	0.3	1.0	3.0	10	30	100
5 5-(1-Hydroxy-2- <i>iso</i> -propyl-amino)-butyl-8-hydroxy-carbostyryl Hydrochloride	0	11.1	30.5	63.3	87.3	100	—	—	—
10 5-(1-Hydroxy-2- <i>iso</i> -propyl-amino)-propyl-8-hydroxy-carbostyryl Hydrochloride	0	5.5	28.3	65.8	89.4	100	—	—	—
(Control)									
Isoproterenol	0	16.6	58.3	83.3	100	—	—	—	—
Salbutamol	0	0	16.6	33.3	66.6	100	—	—	—
15 Metaproterenol Sulphate (Arotec)	0	0	2.7	11.1	27.5	50.0	88.3	100	—
Quinterenol	0	0	0	0	0	0	0	7.6	15.3

20 Further, the acute toxicity was determined with respect to a representative compound of the present invention, 5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy-carbostyryl hydrochloride, using 5 to 6 groups each containing 10 male rats (dd strain; body weight, 18 to 22 g) which had been fasted for 12 hours prior to the test. Salbutamol and *iso* - proterenol were used as controls. The LD₅₀ (50% lethal dose) results are as follows:

25

TABLE 2

LD₅₀ (mg/Kg)

Compound	i.v.	p.o.
30 5-(1-Hydroxy-2-isopropylamino)-butyl-8-hydroxycarbostyryl Hydrochloride	80 (64-100)	2600 (2207-3063)
(Control)		
35 Salbutamol	57.1 (52.7-61.9)	4620* (4160-5130)*
		660 (412.5-1056)
Isoproterenol	112.5 (87.9-144.0)	2587*
40		355 (235.1-536.1)

Note: * — Literature values

The compounds of the present invention can be administered at a dosage level of from 100 to 50 mg/Kg/day by oral, intravenous, intramuscular, intrarectal or inhalation administration in any suitable pharmaceutical dosage form such as a tablet, powder, granule, capsule, syrup, solution, suspension, inhalant (aerosol spray) or suppository, preferably, in combination with pharmaceutically acceptable carriers or diluents such as are well known in the art.

Pharmaceutical compositions generally comprise at least one compound of the present invention and pharmaceutical carriers or diluents such as are commonly employed in conventional pharmaceutical compositions. The composition may contain other active components which do not adversely affect the activities of the compounds of this invention.

Suitable pharmaceutical carriers or diluents include solid carriers such as corn starch, calcium sulphate dihydrate, magnesium stearate, lactose and Aerosil (Registered Trade Mark of Nihon Aerosil Co., Ltd., Japan) which are suitable for use in oral, suppository, injectable and inhalant formulations. The oral dosage forms can be formulated in accordance with well known procedures and conveniently formulated into tablets which can be optionally provided with a sugar coating. Soluble tablets which are suitable for sublingual administration, i.e., troches and lozenges may also be prepared.

The injectable composition can be prepared using physiologically acceptable carriers or diluents in the form of a solution, suspension or dry preparation which is reconstituted instantaneously with a vehicle for injection just before administration.

The compounds of the present invention are advantageously administered in the form of an aerosol spray formulation by inhalation.

Typical examples of suitable formulations are given below, but it is to be noted that other dosage forms can also be prepared using other compounds of this invention according to well-established pharmaceutical techniques.

Formulation 1

Tablets each containing the following components were prepared from the following components:

Component	Amount
5 - (1 - Hydroxy - 2 - isopropyl-amino)ethyl - 8 - hydroxycarbostyryl	1 mg
Corn Starch	70 mg
Magnesium Stearate	9 mg
Lactose	20 mg
Total	100 mg

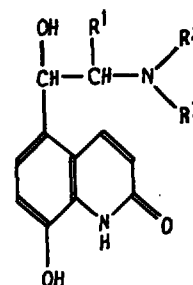
Formulation 2

Aerosol spray for inhalation containing the following components per each dose was prepared and filled in the aerosol dispenser:

Component	Amount
5 - (1 - Hydroxy - 2 - isopropyl-amino)ethyl - 8 - hydroxycarbostyryl	50 mcg
Oleic Acid	10 mcg
Dichlorodifluoromethane	57 mg
Trichlorofluoromethane	25 mg

WHAT WE CLAIM IS:—

1. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivative represented by the following general formula (I):



wherein R¹ represents an alkyl group having 1 to 4 carbon atoms and R² and R³, which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms or a cycloalkyl group having 4 to 6 carbon atoms, or R² and R³ may, when taken together with the nitrogen atom to which they are attached, form a 5- or 6-membered substituted or unsubstituted heterocyclic ring containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms.

2. A derivative according to Claim 1, wherein R² represents a hydrogen atom and R³ represents an alkyl group.

3. A derivative according to Claim 1, wherein R² represents a hydrogen atom and R³ represents an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms.

4. A derivative according to Claim 2 or 3, wherein R¹ represents an alkyl group having from 1 to 3 carbon atoms.

5. A derivative according to Claim 4, wherein R³ represents a benzyl, α - methylbenzyl, α,α - dimethylbenzyl, phenethyl or α,α - dimethylphenethyl group.

6. A derivative according to Claim 1, wherein R² and R³, when taken together with the nitrogen atom to which they are attached form a said heterocyclic ring which contains said one nitrogen atom and optionally, a sulphur or oxygen atom.

The compounds of the present invention can be administered at a dosage level of from 100 to 50 mg/Kg/day by oral, intravenous, intramuscular, intrarectal or inhalation administration in any suitable pharmaceutical dosage form such as a tablet, powder, granule, capsule, syrup, solution, suspension, inhalant (aerosol spray) or suppository, preferably, in combination with pharmaceutically acceptable carriers or diluents such as are well known in the art.

Pharmaceutical compositions generally comprise at least one compound of the present invention and pharmaceutical carriers or diluents such as are commonly employed in conventional pharmaceutical compositions. The composition may contain other active components which do not adversely affect the activities of the compounds of this invention.

Suitable pharmaceutical carriers or diluents include solid carriers such as corn starch, calcium sulphate dihydrate, magnesium stearate, lactose and Aerosil (Registered Trade Mark of Nihon Aerosil Co., Ltd., Japan) which are suitable for use in oral, suppository, injectable and inhalant formulations. The oral dosage forms can be formulated in accordance with well known procedures and conveniently formulated into tablets which can be optionally provided with a sugar coating. Soluble tablets which are suitable for sublingual administration, i.e., troches and lozenges may also be prepared.

The injectable composition can be prepared using physiologically acceptable carriers or diluents in the form of a solution, suspension or dry preparation which is reconstituted instantaneously with a vehicle for injection just before administration.

The compounds of the present invention are advantageously administered in the form of an aerosol spray formulation by inhalation.

Typical examples of suitable formulations are given below, but it is to be noted that other dosage forms can also be prepared using other compounds of this invention according to well-established pharmaceutical techniques.

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Tablets each containing the following components were prepared from the following components:

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Magnesium Stearate	9 mg
Lactose	20 mg
Total	100 mg

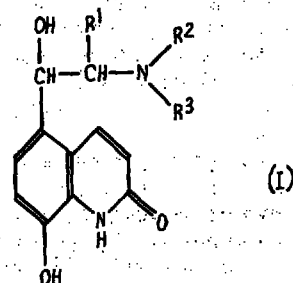
Formulation 2

Aerosol spray for inhalation containing the following components per each dose was prepared and filled in the aerosol dispenser:

Component	Amount
5 - (1 - Hydroxy - 2 - isopropyl-amino)ethyl - 8 - hydroxycarbostyryl	50 mcg
Oleic Acid	10 mcg
Dichlorodifluoromethane	57 mg
Trichlorofluoromethane	25 mg

WHAT WE CLAIM IS:—

1. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivative represented by the following general formula (I):



wherein R¹ represents an alkyl group having 1 to 4 carbon atoms and R² and R³, which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms or a cycloalkyl group having 4 to 6 carbon atoms, or R² and R³ may, when taken together with the nitrogen atom to which they are attached, form a 5- or 6-membered substituted or unsubstituted heterocyclic ring containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms.

2. A derivative according to Claim 1, wherein R² represents a hydrogen atom and R³ represents an alkyl group.

3. A derivative according to Claim 1, wherein R² represents a hydrogen atom and R³ represents an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms.

4. A derivative according to Claim 2 or 3, wherein R¹ represents an alkyl group having from 1 to 3 carbon atoms.

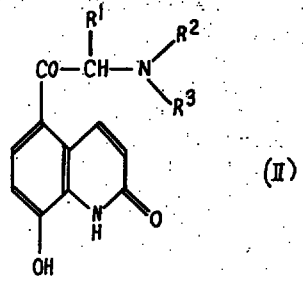
5. A derivative according to Claim 4, wherein R³ represents a benzyl, α - methylbenzyl, α, α - dimethylbenzyl, phenethyl or α, α - dimethylphenethyl group.

6. A derivative according to Claim 1, wherein R² and R³, when taken together with the nitrogen atom to which they are attached form a said heterocyclic ring which contains said one nitrogen atom and optionally, a sulphur or oxygen atom.



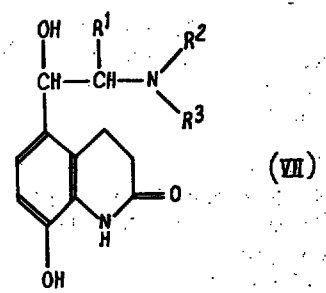
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7. A derivative according to Claim 6, wherein R² and R³, when taken together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino, piperazino, 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.
8. 5 - (1 - Hydroxy - 2 - *iso* - propyl-amino)butyl - 8 - hydroxycarbo-
styryl.
9. 5 - (1 - Hydroxy - 2 - *sec* - butyl-amino)butyl - 8 - hydroxycarbo-
styryl.
10. 5 - (1 - Hydroxy - 2 - ethylamino)-
butyl - 8 - hydroxycarbo-
styryl.
11. 5 - [1 - Hydroxy - 2 - (2 - phenethyl-
amino)]butyl - 8 - hydroxycarbo-
styryl.
12. 5 - (1 - Hydroxy - 2 - *iso* - propyl-
amino)propyl - 8 - hydroxycarbo-
styryl.
13. 5 - (1 - Hydroxy - 2 - *tert* - butyl-
amino)propyl - 8 - hydroxycarbo-
styryl.
14. An acid addition salt of a deriva-
tive as claimed in any preceding Claim.
15. An acid addition salt according to
Claim 14, which is a hydrochloride, a sul-
phate, a phosphate, a maleate, a fumarate or
an oxalate.
16. A process for preparing 1 5 - 1 -
hydroxy - 2 - (substituted - amino)alkyl -
8 - hydroxycarbo-
styryl derivative of the
general formula (I) defined in any of Claims
1 to 7, or an acid addition salt thereof,
which comprises reducing a 5 - (α - sub-
stituted - aminoalkanoyl) - 8 - hydroxycarbo-
styryl of the following general formula (II):



- wherein R¹, R² and R³ are as defined in
any of Claims 1 to 7, or an acid addition
salt with hydrogen in the presence of a cata-
lyst or with a reducing agent.
17. A process according to Claim 16,
wherein the reduction is effected by using
palladium black, palladium-on-carbon,
platinum oxide or Raney nickel as a cata-
lyst in an amount of from 0.05 to 1 mole
per mole of the derivative of general formula
(II) at a temperature of from room tem-
perature to 150°C under a hydrogen atmos-
phere at a pressure of from atmospheric
pressure to 100 atmospheres.
18. A process according to Claim 17,
wherein the catalyst is used in an amount of
from 0.1 to 0.5 mole per mole of the deriva-
tive of general formula (II).
19. A process according to Claim 17 or
18, wherein the temperature is from room
temperature to 120°C.

20. A process according to any of Claims
17 to 19, wherein the pressure is from
atmospheric to 50 atmospheres.
21. A process according to any of Claims
17 to 20, wherein the reduction is effected
in the presence of water or methanol ethanol
or *iso* - propanol as a solvent.
22. A process according to Claim 16,
wherein the reduction is effected by using
lithium aluminium hydride or sodium boro-
hydride as a reducing agent in an amount of
from 2 to 10 moles per mole of the deriva-
tive of general formula (II) at a temperature
of from 0° to 100°C under atmospheric pres-
sure.
23. A process according to Claim 22,
wherein the reducing agent is used in an
amount of from 2 to 5 moles per mole of the
derivative of general formula (II).
24. A process according to Claim 22 or
23, wherein the temperature is from 20° to
50°C.
25. A process according to any of Claims
22 to 24, wherein lithium aluminium hydride
is employed as the reducing agent and the
reduction is effected in the presence of an-
hydrous ethyl ether, ethyl acetate or tetra-
hydrofuran as a solvent.
26. A process according to any of Claims
22 to 25, wherein sodium borohydride is
employed as the reducing agent and the re-
duction is effected in the presence of water
or methanol, ethanol, *n* - propanol, or *iso* -
propanol as a solvent.
27. A process for preparing a 5 - [1 -
hydroxy - 2 - (substituted - amino)]alkyl -
8 - hydroxycarbo-
styryl derivative of the
general formula (I) defined in Claim 1, or
an acid addition salt thereof, substantially as
hereinbefore described with reference to any
one of the foregoing Examples 9 to 12.
28. A process for preparing a 5 - [1 -
hydroxy - 2 - (substituted - amino)]alkyl -
8 - hydroxycarbo-
styryl derivative of the
general formula (I) defined in any of Claims
1 to 7, which comprises dehydrogenating a
5 - [1 - hydroxy - 2 - (substituted - amino)]-
alkyl - 8 - hydroxy - 3,4 - dihydrocarbo-
styryl derivative of the following general formula
(VII):



- wherein R¹, R² and R³ are as defined in any
of Claims 1 to 7.
29. A process according to Claim 28,



wherein tetrachloro - 1,4 - benzoquinone or dichloro - dicyano - 1,4 - benzoquinone is employed as a dehydrogenating agent.

30. A process according to Claim 29, wherein the dehydrogenating agent is employed in an amount of from 1 to 5 moles per mole of the derivative of general formula (VII).

31. A process according to Claim 28, wherein palladium black, platinum black, platinum oxide or Raney nickel is employed as a dehydrogenation catalyst.

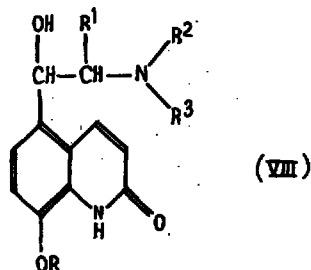
32. A process according to Claim 31, wherein the catalyst is used in an amount of from 0.5 to 3 moles per mole of the derivative of general formula (VII).

33. A process according to any of Claims 28 to 32, wherein the dehydrogenation is effected in benzene, toluene, xylene, phenetol, chlorobenzene, methanol, ethanol, *iso* - propanol, *tert* - butanol, dioxane, acetone, water or acetic acid as a solvent.

34. A process according to any of Claims 28 to 33, wherein the dehydrogenation is effected at a temperature of from room temperature to the reflux temperature of the reaction system.

35. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivative of the general formula (I) defined in Claim 1, substantially as hereinbefore described with reference to the foregoing Example 13.

36. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl of the general formula (I) defined in Claim 1, which comprises dealkylating with a hydrohalic acid a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - alkoxycarbostyryl of the following general formula (VIII):



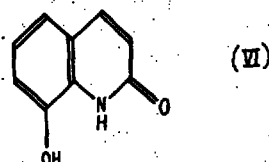
wherein R¹, R² and R³ are as defined in Claim 1 and R represents an alkyl group having from 1 to 6 carbon atoms.

37. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivative of the general formula (I) defined in Claim 1, substantially as hereinbefore described with reference to the foregoing Example 4.

38. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarbostyryl derivative of the

general formula (I) defined in any of Claims 1 to 7 which comprises the steps of:

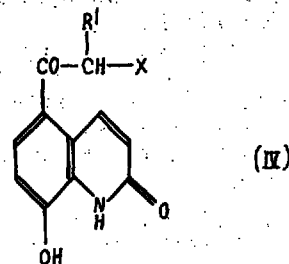
(1) reacting 8 - hydroxycarbostyryl of the following general formula (VI):



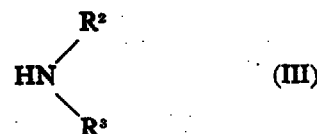
with an α - halo - alkanolic acid halide of the following general formula (V):



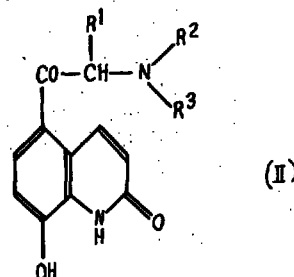
wherein R¹ represents an alkyl group having 1 to 4 carbon atoms, and X and X' may be the same or different and each represents a halogen atom, in the presence or absence of a solvent and in the presence of a Lewis acid catalyst, to obtain a 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl derivative of the following general formula (IV):



wherein R¹ and X are as defined above, (2) reacting the 5 - (α - haloalkanoyl) - 8 - hydroxycarbostyryl thus obtained with ammonia or an amine of the following general formula (III):



wherein R² and R³ are as defined above, in the presence or absence of a solvent, to obtain a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyryl of the following general formula (II):



wherein R¹, R² and R³ are as defined above, and

(3) reducing the 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarboxystyryl of the general formula (II) with hydrogen in the presence of a hydrogenation catalyst or with a reducing agent.

39. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarboxystyryl derivative of the general formula (I) defined in Claim 1, substantially as hereinbefore described.

40. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarboxystyryl derivative according to claim 1, when prepared by a process as claimed in any of Claims 16 to 39.

41. A pharmaceutical composition which comprises a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxycarboxystyryl as claimed in any of Claims 1 to 15 or 40, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

42. A pharmaceutical composition according to Claim 41 and in a formulation suitable for inhalation in the form of an aerosol spray.

43. A pharmaceutical composition according to Claim 41 and in tablet form.

44. A pharmaceutical composition substantially as hereinbefore described with reference to the foregoing Formulation 1 or 2 of the invention.

45. A pharmaceutical composition according to Claim 41 and substantially as hereinbefore described.

46. A method of stimulating the activity of β - adreno - receptor by administering to a non-human mammal a pharmaceutically effective amount of a pharmaceutical composition as claimed in any of Claims 41 to 45.

47. A method of alleviating bronchial asthma, which comprises administering to a non-human mammal a pharmaceutically effective amount of a pharmaceutical composition as claimed in any of Claims 41 to 43.

48. A method of alleviating bronchial asthma, according to Claim 47 and substantially as hereinbefore described with reference to the foregoing Reference Example.

49. An aerosol dispenser containing a pharmaceutical composition as claimed in Claim 42.

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