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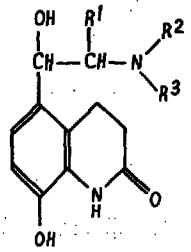
(54) 5-SUBSTITUTED ALKYL-8-HYDROXYCARBOSTYRIL DERIVATIVES AND PRODUCTION THEREOF

(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 - hydroxy - 3,4 - dihydrocarbostyril derivatives, to acid addition salts thereof and to a process for preparing them.

It is well known that certain carbostyril 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 - hydroxy - 3,4 - dihydrocarbostyril derivatives having the following general formula (I):



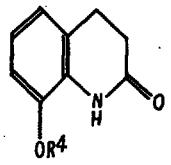
(I)

wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and R^2 and R^3, 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 R^2 and R^3 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.

This invention also provides a process for preparing the above 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivatives represented by the formula (I) above, and acid addition salts thereof which comprises the steps of:

(1) reacting a 8 - substituted - 3,4 - dihydrocarbostyril of the following general formula (VI):



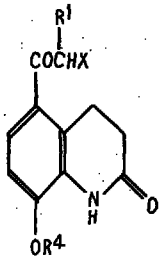
(VI)

wherein R^4 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, with an α - haloalkanoic acid of the following general formula (V):



(V)

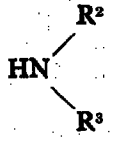
wherein R^1 is as defined above and X and X', which may be the same or different, each represents a halogen atom, in the presence or absence of a solvent and in the presence of a Lewis acid catalyst, to produce a corresponding 5 - (α - haloalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyril of the following general formula (IV):



(IV)

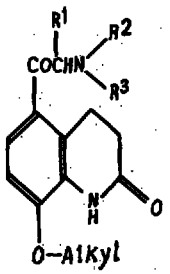
wherein R^1, R^4 and X are as defined above,

(2) reacting the resulting 5 - (α - haloalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyril of the formula (IV) with ammonia or an amine of the following general formula (III):



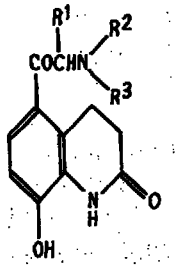
(III)

wherein R^2 and R^3 are as defined above, to produce a 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril of the following general formula (IIa):



(IIa)

wherein "Alkyl" represents an alkyl group having 1 to 4 carbon atoms and R^1, R^2, and R^3 are as defined above, or a 5 - (α - substituted aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IIb):



(IIb)

wherein R^1, R^2, and R^3 are as defined above, and dealkylating the 8 - alkoxy - dihydrocarbostyril of the formula (IIa) with a hydrogen halide to produce the 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IIb), and

(3) reducing the resulting 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril with hydrogen in the presence of a hydrogenation catalyst or with a reducing agent.

The 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl 8 - hydroxy - 3,4 - dihydrocarbostyril derivatives of the 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; particularly for treating bronchial asthma.

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

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" used herein means heterocyclic groups containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms such as a pyrrolidino, piperidino, morpholino, or piperazino 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 compounds of the present invention represented by the formula (I) may be prepared from 8 - hydroxy - 3,4 - dihydrocarbostyril according to the reaction scheme shown in the single Figure of the accompanying drawings, wherein R^1, R^2, R^3, R^4, X and X′ are as hereinbefore defined.

The 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VI) used as a starting material in the preparation of the compounds of the formula (IV) is a known compound and may easily be prepared by, for example, the method as disclosed in J. D. Loudon and J. Ogg; *J. Chem. Soc.*, 1955, 739 or Fritz Mayer, L. van Zutphen and H. Philips, *Ber.*, 60, 858 (1927).

The process according to the present invention will be hereinafter illustrated in greater detail.

The α - haloalkanoic acid halide of the formula (V) which can be used in the present invention as a reactant in the preparation of the compound of the formula (IV) includes α - chloropropionyl chloride, α - bromopropionyl chloride, α - chlorobutyryl chloride, α - bromobutyryl chloride, α - bromobutyryl bromide and α - chlorovaleryl chloride, and is preferably α - chloropropionyl chloride or α - chlorobutyryl chloride. The reaction between the 3,4 - dihydrocarbostyril of the formula (VI) and the α - haloalkanoic acid halide of the formula (V) is a so-called Friedel-Crafts reaction.

The catalyst which can be used in this reaction is a Lewis acid, for example, aluminium chloride or bromide, zinc chloride, ferric chloride, stannic chloride, titanium chloride or boron trifluoride, aluminium chloride being preferred. The catalyst is generally used in an amount of from 2 to 10 moles, preferably 3 to 6 moles, per mole of the compound of the formula (IV).

This reaction can be effected either in the absence of a solvent or in the presence of an inert organic solvent. Suitable examples of solvents which can be used in this reaction are carbon disulphide, nitrobenzene, diethyl ether and dioxane, preferably, carbon disulphide. These solvents are usually used in a volume of from 0.5 to 20, preferably from 2 to 10, times the volume of the reactants.

This reaction is generally conducted using from an equimolar amount to a large excess of the α - haloalkanoic acid halide of the formula (V) preferably 2 to 20 moles, more preferably from 2 to 10 moles, of the α - haloalkanoic acid halide of the formula (V) per mole of the 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VI). The reaction proceeds at from room temperature (about 20 to 30°C) to 150°C, preferably from room temperature to 80°C. The reaction time varies depending upon the reaction temperature employed, but is usually from 1 to 20, preferably from 1 to 10 hours. The reaction is preferably carried out under anhydrous conditions.

The amine of the formula (III) which can be used as a reactant in the preparation of the 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyrils of the formulae (IIa) and (IIb) includes 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.

The reaction between the 5 - (α - haloalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyril intermediate of the formula (IV) and ammonia or the amine of the formula (III) can be carried out either in the absence of a solvent because the amine of the formula (III) *per se* serves as a reaction solvent, or in the presence of an appropriate solvent. Suitable examples of solvents which can be used in this reaction include lower alcohols such as methanol, ethanol and *iso* - propanol, 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 *iso* - propanol are preferably used.

This reaction can be effected using from an equimolar amount to a large excess of ammonia or the amine of the formula (III), preferably from 2 to 10 moles of the amine of the formula (III) per mole of the 5 - (α - haloalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IV) at from room temperature to the refluxing temperature of the reaction system, preferably from 40 to 100°C at from atmospheric

pressure to 10 atmospheres. When the reaction is effected without using any solvent, it is preferable to use a large excess of ammonia the amine of the formula (III) with respect to the carbostyril derivative of the formula (IV).

When the 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (VI) wherein R^4 is a hydrogen atom is used as a starting material, a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IIb) is obtained, which can be subjected to a subsequent reduction reaction to produce the 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydroxycarbostyril of the formula (I). When an 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (VI) wherein R^4 is an alkyl group is used as a starting material, a corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (IIa) is obtained. The resulting 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (IIa) is then reacted with a hydrogen halide to dealkylate the 8-position of the 3,4 - dihydrocarbostyril moiety thereby obtaining the compound of the formula (IIa), which can be subjected to the subsequent reduction reaction as indicated above.

The hydrogen halide used in this dealkylation includes, for example, hydrogen bromide, hydrogen chloride, and hydrogen iodide, and is preferably hydrogen bromide. These hydrogen halides can advantageously be employed in an appropriate solvent such as methanol, ethanol or, propanols, but preferably in water in the form of an aqueous solution of the hydrogen halide at a concentration of from 10 to 50%, preferably 47% hydrogen bromide.

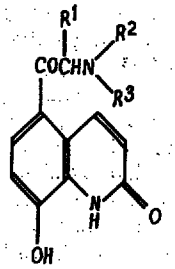
This dealkylation reaction can generally be carried out using the hydrogen halide in from an equimolar amount to, preferably, a large excess with respect to the compound of the formula (IIa) by heating at a temperature of from 100 to 150°C, preferably at reflux, for from 1 to 20 hours, preferably from 3 to 10 hours.

The reduction of the above obtained 5 - substituted - aminoalkanoyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the formula (IIb) to the 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the formula (I) may be conducted using a reducing agent such as lithium aluminium hydride or sodium borohydride, or a 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.

A reducing agent may be used in an amount of from 2 to 10 moles, preferably from 2 to 5 moles, per mole of the carbostyril compound of the formula (IIb) 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 an alcohol 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 carbostyril compound of the formula (IIb) 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.

Alternatively, the compound of the formula (I) of the present invention may be prepared by catalytically reducing the corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril derivative having the following general formula (VII):



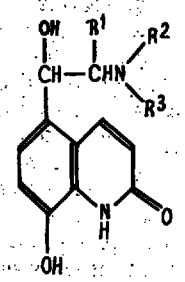
(VII)

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

The 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril derivative of the formula (VII) which may be used as a reactant in the above described reduction and a process for preparing the same are described and claimed in our co-pending Patent Application No. 28863/77, (Serial No. 1496874), of even date.

The catalytic reduction initially results in the production of a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril having the formula (IIb) as described hereinbefore, which is then subjected to further reduction to form a compound of the formula (I) or a 5 - (1 - hydroxy - 2 -

substituted - aminoalkyl) - 8 - hydroxycarbostyril of the following general formula (VIII):



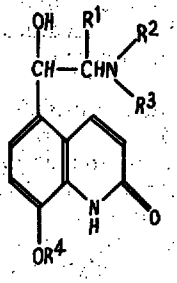
(VIII)

wherein R^1, R^2, and R^3 are as defined above. Compounds of the general formula (VIII) and a process for their preparation are also described and claimed in our co-pending Patent Application No. 55897/74, (Serial No. 1496766) of even date.

The compounds of the formulae IIa and IIb form the subject of our copending Patent Application No. 28864/77, (Serial No. 1496875) of even date.

The reduction of the 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril derivative of the formula (VII) to the compound of the formula (I) may be carried out in a solvent such as water, methanol, ethanol, *iso* - propanol or ethyl acetate, in the presence of a catalyst, e.g., palladium black, platinum oxide, palladium-on-carbon, platinum black or Raney nickel and the like at from room temperature to 150°C, preferably from room temperature to 120°C in a hydrogen atmosphere of from 1 to 100, preferably from 1 to 50 atmospheres.

A compound of the general formula (I) may also be prepared by dealkylating with a hydrogen halide a corresponding 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative represented by the following general formula (IX):



(IX)

wherein R^1, R^2, R^3, and R^4 are as defined above.

The 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 3,4 - dihydrocarbostyril derivatives of the general formula (IX) above and the process for preparing them are described and claimed in our co-pending Patent Application No. 55929/74, (Serial No. 1496770) of even date.

This dealkylation can be carried out under the same reaction conditions as used in respect of the dealkylation of the compound (IIa).

Both the compounds of the formula (IIb) and the compounds of the 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 with 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 dissolved in an appropriate organic solvent such as methanol, ethanol, *iso* - propanol or acetone.

Both the free bases of the compounds (I) and the acid addition salts thereof exhibit a stimulating activity on β - adrenoreceptor and, therefore, are very useful as pharmaceuticals for treating disorders such as bronchial asthma. As is apparent to one skilled in the art, the compounds (I) of the present invention contain two asymmetrical centres and, therefore, can be present in four optically active forms. Particularly preferred compounds of the formula (I) are the following basic compounds and their hydrochlorides, sulphates, phosphates, maleates, fumarates and oxalates:

5 - (1 - Hydroxy - 2 - *iso* - propylamino)-propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril,

5 - (1 - Hydroxy - 2 - *iso* - propylamino)-butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril,

5 - (1 - Hydroxy - 2 - *tert* - butylamino)-butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril,

5 - (1 - Hydroxy - 2 - *sec* - butylamino)-butyl - 8 hydroxy - 3,4 - dihydrocarbostyril,

5 - (1 - Hydroxy - 2 - *tert* - butylamino)-propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril,

5 - (1 - Hydroxy - 2 - ethylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

The present invention will now be described by reference to the following Examples, but these examples are given for the purpose of illustration and not to be construed as limiting the scope of the invention. Unless otherwise indicated, all parts, percentages and ratios are by weight.

EXAMPLE 1

17.1 Grams of α - bromopropionyl chloride (V), 27 g of anhydrous aluminium chloride and 8 ml of nitrobenzene were added to 8 g of 8 - methoxy - 3,4 - dihydrocarbostyril (VI), and the mixture was heated at a temperature of 50 to 60°C for one hour while stirring. The reaction mixture was then poured into 200 ml of ice-water, and the precipitate formed was filtered off and washed with water. The precipitate was then recrystallized from ethanol to obtain 11.5 g of a material having a melting point of 154—155°C. The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - bromopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV).

EXAMPLE 2

26.4 Grams of α - bromobutyryl bromide (V), 17.5 g of anhydrous aluminium chloride and 5 ml of nitrobenzene were added to 5 g of 8 - methoxy - 3,4 - dihydrocarbostyril (VI), and the mixture was heated at a temperature of 50 to 60°C for one hour while stirring. The reaction mixture was then poured into 100 ml of ice-water, and the precipitate formed was filtered off and washed with water. The precipitate was then recrystallized from ethanol to obtain 5 g of a material having a melting point of 151—152°C. The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - bromobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV).

EXAMPLE 3

2 Grams of the 5 - (α - bromopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 1 were suspended in 50 ml of *iso* - propanol, 5 grams of *iso* - propylamine were added and the suspension was stirred for 2 hours at a temperature of 60°C. The solvent was then distilled off, and the resulting residue was dissolved in 5 ml of *iso* - propanol. The solution was then adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The precipitate formed was filtered and a mixture of acetone and diethyl ether was added to the filtrate. The precipitate formed was filtered off and recrystallized from *iso* - propanol to obtain 1.5 g of a white amorphous material having a melting point of 172 to 174°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *iso* - propylaminopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride dihydrate.

EXAMPLE 4

5 Grams of 5 - (α - bromopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 1 were suspended in 50 ml of *iso* - propanol, and 10 g of *t* - butylamine (III) were added to the suspension followed by stirring the mixture at a temperature of 60°C for 15 hours. The solvent was then distilled off, and the resulting residue was dissolved in 10 ml of *iso* - propanol. The solution was then adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The precipitate formed was filtered off and acetone was added to the filtrate. The precipitate formed was filtered, and diethyl ether was added to the filtrate. The precipitate formed was filtered off and recrystallized from a mixture of *iso* - propanol and diethyl ether to obtain 2.1 g of a colourless amorphous material having a melting point of 207 to 210°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *t* - butylaminopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride monohydrate.

EXAMPLE 5

2 Grams of 5 - (α - bromobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 2 were suspended in 50 ml of *iso* - propanol, 5 g of *iso* - propylamine (III) were added to the suspension, and the mixture was stirred at a temperature of 60°C for 4 hours. The solvent was then distilled off, and the resulting residue was dissolved in 5 ml of *iso* - propanol. The solution was then adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The precipitate formed was filtered off and recrystallized from a mixture of *iso* - propanol and acetone to obtain 1.7 g of a colourless amorphous material having a melting point of 204 to 206°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 (α - *iso* - propylaminobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride monohydrate.

EXAMPLE 6

3 Grams of 5 - (α - bromobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 2 were suspended in 50 ml of *iso* - propanol, 9 g of *t* - butylamine (III) were added to the suspension and the mixture was stirred at a temperature of 60°C for 19 hours. The solvent was then distilled off, and the resulting residue was dissolved in 5 ml of *iso* - propanol. The solution was then adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The precipitate formed was filtered, and acetone was added to the filtrate. The precipitate formed was filtered and di-

ethyl ether was added to the filtrate. The precipitate formed was filtered off and recrystallized from *iso* - propanol to obtain 1.6 g of a colourless amorphous material having a melting point of 160 to 162°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *t* - butylaminobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride monohydrate.

EXAMPLE 7

1.5 Grams of 5 - (α - *iso* - propylaminopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) prepared as described in Example 4 were dissolved in 15 ml of a 47% aqueous hydrobromic acid and the solution was refluxed for 15 hours under heating at a temperature of 140°C. The reaction mixture was concentrated, and acetone was added to the reaction mixture to crystallize the product. The product was then recrystallized from a mixture of ethanol and acetone to obtain 1.1 g of a material having a melting point of 223 to 226°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spetral analyses and elemental analysis to be 5 - (α - *iso* - propylaminopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrobromide.

EXAMPLE 8

1.5 Grams of 5 - (α - *iso* - propylaminobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) were dissolved in 15 ml of a 47% aqueous hydrobromic acid and the solution was refluxed for 15 hours under heating at a temperature of 130 to 140°C. The reaction mixture was concentrated, and acetone was added to the reaction mixture to crystallize the product. The product was then recrystallized from a mixture of ethanol and acetone to obtain 1.0 g of a material having a melting point of 165 to 168°C. The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *iso* - propylaminobutyryl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrobromide 1/2 hydrate.

EXAMPLE 9

1 Gram of 5 - (α - *t* - butylaminopropionyl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) obtained from the hydrochloride monohydrate prepared as described in Example 4 was dissolved in 15 ml of a 47% aqueous hydrobromic acid and the solution was refluxed for 15 hours under heating at a temperature of 140 to 150°C. The reaction mixture was concentrated, and acetone was added to the reaction mixture to crystallize the product. The product was then recrystallized from a mixture of ethanol and acetone to obtain 0.7 g of a material having a melting point of 224 to 227°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *t* - butylaminopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrobromide (IIb) monohydrate.

EXAMPLE 10

1.5 Grams of 5 - (α - *t* - butylaminobutyryl) - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) obtained from the hydrochloride moonhydrate prepared as described in Example 6 were dissolved in a 47% aqueous hydrobromic acid and the solution was refluxed for 19 hours at a temperature of 140 to 150°C. The reaction mixture was concentrated, and acetone was added to the reaction mixture to crystallize the product. The product was then recrystallized from a mixture of ethanol and acetone to obtain 1.1 g of a material having a melting point of 144 to 146°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - (α - *t* - butylaminobutyryl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrobromide dihydrate.

EXAMPLE 11

5 Grams of 5 - (α - bromopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril were suspended in 30 ml of benzene, and 4.2 ml of morpholine were added to the suspension. The mixture was allowed to react for 4 hours while heating under refluxing. The reaction mixture was filtered and the filtrate was washed with water followed by concentration under reduced pressure to remove any remaining water. The resulting residue was dissolved in 50 ml of *iso* - propanol, and the solution was adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The viscous precipitate which formed upon ice-cooling was separated and dissolved in acetone by heating. After allowing the solution to cool, the precipitate formed was dissolved in 30 ml of water and adjusted to a pH of 7.5 to 8 with sodium bicarbonate. The precipitate formed upon ice-cooling was filtered and dissolved in 10 ml of a 47% aqueous hydrobromic acid followed by concentration under reduced pressure. The residue thus obtained was washed with 10 ml of ethanol and recrystallized from ethanol to obtain 2.6 g of white amorphous 5 - (α - morpholinopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrobromide (IIb) monohydrate having a melting point of 235 to 236°C (with decomposition).

EXAMPLE 12

1.0 Gram of 5 - (α - *iso* - propylaminopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) obtained from the hydrobromide 1/2 hydrate prepared as described in Example 8 was dissolved in 50 ml of methanol, 0.3 g of sodium borohydride was added slowly to the solution while ice-cooling and the mixture was stirred at room temperature for one hour. Methanol which had been saturated with hydrogen chloride gas was then added to the mixture to adjust the mixture to a pH of 1 to 2. The precipitate formed was filtered off, and the filtrate was concentrated to dryness. A 1N aqueous sodium hydroxide solution was then added to the residue to attain a pH of 7.5 to 8, and the precipitate formed was filtered and dissolved in ethanol and then hydrogen chloride gas was bubbled into the solution. The precipitate formed was filtered and recrystallized from ethanol to obtain 0.8 g of a material having a melting point of 211 to 213°C. 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 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride 1/2 hydrate.

EXAMPLE 13

To 1.0 Gram of 5 - (α - *iso* - propylaminobutyryl - 8 hydroxy - 3,4 - dihydrocarbostyril (IIb) were added 20 ml of ethanol and 0.05 g of platinum oxide, and the mixture was reduced under a hydrogen pressure of 2 atmospheres at a temperature of 60°C for 10 hours. After completion of the reduction, the catalyst was removed by filtration, and the filtrate was adjusted to a pH of 1 with concentrated hydrochloric acid and concentrated to dryness. The resulting residue was recrystallized from ethanol to obtain 0.9 g of a material having a melting point of 196 to 198°C. 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)-butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride monohydrate.

EXAMPLE 14

To 1.0 g of 5 - (α - *tert* - butylaminopropionyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrobromide obtained from the corresponding monohydrate prepared in Example 9 were added 50 ml of water and 0.2 g of palladium black, and the mixture was reduced under a hydrogen pressure of 1 atmosphere at a temperature of 60°C for 20 hours. After completion of the reduction, the catalyst was filtered off and the filtrate was concentrated to dryness. The resulting residue was recrystallized from ethanol to obtain 0.75 g of a material having a melting point of 198 to 199°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 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrobromide monohydrate.

EXAMPLE 15

To 1.0 Gram of 5 - (α - *tert* - butylaminobutyryl) - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrobromide (IIb) obtained from the corresponding dihydrate prepared in Example 10 were added 50 ml of water and 0.2 g of palladium black, and the mixture was reduced under a hydrogen pressure of 1 atmosphere at a temperature of 80°C for 10 days. After completion of the reduction, the catalyst was filtered off, and the filtrate was concentrated to dryness. The resulting residue was recrystallized from ethanol 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 - *tert* - butylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrobromide (as an ethanol solvate).

EXAMPLE 16

To 2 g of 5 - (α - *iso* - propylaminobutyryl) - 8 - hydroxycarbostyril (VII) were added 0.1 g of palladium black and 50 ml of ethanol, and the mixture was reduced at a hydrogen pressure of 35 atmospheres at a temperature of 75°C for 15 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered off, and the filtrate was adjusted to a pH of 1 with concentrated hydrochloric acid. The mixture was then concentrated to dryness and the resulting precipitate was recrystallized from ethanol to obtain 1.7 g of 5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride monohydrate having a melting point of 196 to 198°C.

EXAMPLE 17

To 1 Gram of 5 - (α - *iso* - propylaminobutyryl) - 8 hydroxycarbostyril hydrochloride (VII) were added 0.05 g of platinum black and 100 ml of water, and the mixture was reduced at a hydrogen pressure of 40 atmospheres at a temperature of 60°C for 18 hours with shaking of the mixture. After completion of the reduction, the catalyst was filtered, and the filtrate was concentrated to dryness. The precipitate formed was then recrystallized from *iso* - propanol to obtain 0.85 g of 5 - (1 - hydroxy - 2 - *iso* - propylamino) - butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride monohydrate having a melting point of 196 to 198°C.

EXAMPLE 18

To 0.5 Gram of 5 - (α - *sec* - butylaminobutyryl) - 8 - hydroxycarbostyril (VII) were added 0.0025 g of palladium black and 15 ml of ethanol, and the mixture was reduced at a hydrogen pressure of 50 atmospheres at a temperature of 80°C for 15 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered, and the filtrate was adjusted to a pH of 1 with concentrated hydrochloric acid and concentrated to dryness. The precipitate formed was then recrystallized from ethanol to obtain 0.45 g of 5 - (1 - hydroxy - 2 - *sec* - butylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrochloride monohydrate having a melting point of 205 to 207°C.

EXAMPLE 19

15 Millilitres of a 47% aqueous hydrobromic acid was added to 1.5 g of 5 - (1 - hydroxy - 2 - *tert* - butylamino)propyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IX), and the mixture was heated under reflux for a period of 15 hours. Thereafter, acetone was added to the reaction mixture to crystallize the product, and the resulting crystals were recrystallized from a mixture of ethanol and acetone to obtain 1.4 g of a material having a melting point of 198 to 199°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 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrobromide monohydrate.

In the same manner as described in Example 19, the following compounds of the formula (I) were prepared from the corresponding 8 - methoxy compounds of the formula (IX).

5 - [1 - Hydroxy - 2 - (2 - phenethylamino)]butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrochloride having a melting point of 127 to 129°C (with decomposition)

5 - (1 - Hydroxy - 2 - morpholino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrobromide having a melting point of 183 to 185°C (with decomposition)

5 - (1 - Hydroxy - 2 - ethylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrochloride having a melting point of 213 to 214.5°C (with decomposition).

EXAMPLE 20

To 1.0 Gram of 5 - (α - *tert* - butylaminobutyryl) - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrobromide (IIb) were added 50 ml of water and 0.2 g of palladium black, and the mixture was reacted at a hydrogen pressure of 1 atmosphere at a temperature of 80°C for 10 days. After completion of the reduction, the catalyst was filtered off, and the filtrate was concentrated to dryness. The resulting residue was recrystallized from ethanol 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 - *tert* - butylamino)butyl 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrobromide (as an ethanol solvate).

EXAMPLE 21

1.0 Gram of 5 - (2 - morpholinobutyryl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrobromide was dissolved in 70 ml of water and 0.2 g of palladium-on-carbon and 0.3 g of palladium black were added to the solution. The mixture was catalytically reduced under atmospheric pressure in a hydrogen atmosphere for 10 days at a temperature of 70°C while shaking. After completion of the reduction, the reaction mixture was filtered to remove the catalysts, and the filtrate was concentrated to dryness under reduced pressure. The resulting residue was dissolved in acetone by heating and the solution allowed to cool. The precipitate formed upon cooling was recrystallized from ethanol to obtain 0.7 g of white amorphous 5 - (2 - morpholino - 1 - hydroxybutyl) - 8 hydroxy - 3,4 - dihydrocarbostyril (I) hydrobromide 1/2 hydrate having a melting point of 183 to 185°C (with decomposition). The product thus obtained was confirmed by NMR and IR spectral analyses and by elemental analysis.

REFERENCE EXAMPLE

The stimulating activity of the compound (I) 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 its trachea. Artificial respiration was conducted using a device according to the Konzett-Rössler method (Konzett H. & Rössler R., "Versuchsanordnung zu Untersuchungen and der Branchial Moskolatur", *Arch. Exp. Path., Pharmack, 195,* 71—74, 27—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 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.

TABLE 1

Bronchial Resistance (%)

Compound	Dosage Level (g/kg)								
	0.01	0.03	0.1	0.3	1.0	3.0	10	30	100
5-(1-Hydroxy-2-isopropyl-amino)-butyl-8-hydroxy-carbostyril Hydrochloride	0	13.5	33.7	73.2	92.3	100	–	–	–
5-(1-Hydroxy-2-tert-butyl-amino)-propyl-8-hydroxy-carbostyril Hydrochloride	0	5.7	21.4	65.0	81.8	100	–	–	–
(Control)									
Isoproterenol	0	16.6	58.3	83.3	100	–	–	–	–
Salbutamol	0	0	16.6	33.3	66.6	100	–	–	–
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

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 or inhalation administration in a conventional 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 which 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 compound 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 may be formulated in accordance with well known procedures and are conveniently formulated into tablets which can be optionally provided with a sugar coating. Soluble tablets suitable for sublingual administration, i.e., troches or lozenges, may also be prepared.

An injectable composition may 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 may 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:

Components	Amount
5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril	1 mg
Corn Starch	70 mg
Magnesium stearate	9 mg
Lactose	20 mg
Total	100 mg

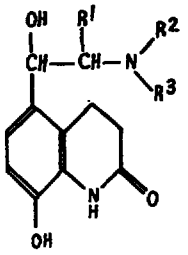
Formulation 2

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

Components	Amount
5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril	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 - hydroxy - 3,4 - dihydrocarbostyril derivative of the following general formula (I):



(I)

wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and R^2 and R^3, 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 R^2 and R^3 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 R^2 represents a hydrogen atom and R^3 represents an alkyl group having 1 to 4 carbon atoms.

3. A derivative according to Claim 2, wherein R^1 represents an alkyl group having 1 to 3 carbon atoms.

4. A derivative according to Claim 1, wherein R^1 represents an alkyl group having 1 or 2 carbon atoms, R^2 represents a hydrogen atom and R^3 represents said aralkyl group.

5. A derivative according to Claim 4, wherein R^3 represents a benzyl, α - methylbenzyl, α,α - dimethylbenzyl, phenethyl or α,α - dimethylphenethyl group.

6. A derivative according to Claim 1, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered substituted or unsubstituted heterocyclic ring optionally containing an oxygen or sulphur atom.

7. A derivative according to Claim 6, wherein said heterocyclic group is a pyrrolidino, piperidino, morpholino, piperazino, 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

8. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

9. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

10. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

11. 5 - (1 - Hydroxy - 2 - *sec* - butylamino)butyl - 8 - hydroxy - 3,4 -dihydrocarbostyril.

12. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

13. 5 - (1 - Hydroxy - 2 - ethylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

14. 5 - [1 - Hydroxy - 2 - (2 - phenethylamino)butyl] - 8 - hydroxy - 3,4 - dihydrocarbostyril.

15. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

16. 5 - (1 - Hydroxy - 2 - morpholino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

17. An acid addition salt of an 8 - hydroxycarbostyril derivative as claimed in any preceding Claim.

18. An acid addition salt according to Claim 17, which is a hydrochloride, a sulphate, a phosphate, a maleate, a fumarate or an oxalate.

19. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril 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 - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the following general formula (IIb):

Formulation 1

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

Components	Amount
5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril	1 mg
Corn Starch	70 mg
Magnesium stearate	9 mg
Lactose	20 mg
Total	100 mg

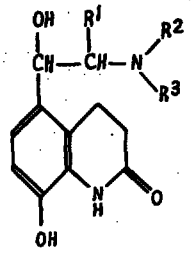
Formulation 2

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

Components	Amount
5 - (1 - hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril	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 - hydroxy - 3,4 - dihydrocarbostyril derivative of the following general formula (I):



(I)

wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and R^2 and R^3, 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 R^2 and R^3 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 R^2 represents a hydrogen atom and R^3 represents an alkyl group having 1 to 4 carbon atoms.

3. A derivative according to Claim 2, wherein R^1 represents an alkyl group having 1 to 3 carbon atoms.

4. A derivative according to Claim 1, wherein R^1 represents an alkyl group having 1 or 2 carbon atoms, R^2 represents a hydrogen atom and R^3 represents said aralkyl group.

5. A derivative according to Claim 4, wherein R^3 represents a benzyl, α - methylbenzyl, α,α - dimethylbenzyl, phenethyl or α,α - dimethylphenethyl group.

6. A derivative according to Claim 1, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered substituted or unsubstituted heterocyclic ring optionally containing an oxygen or sulphur atom.

7. A derivative according to Claim 6, wherein said heterocyclic group is a pyrrolidino, piperidino, morpholino, piperazino, 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

8. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

9. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

10. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

11. 5 - (1 - Hydroxy - 2 - *sec* - butylamino)butyl - 8 - hydroxy - 3,4 -dihydrocarbostyril.

12. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

13. 5 - (1 - Hydroxy - 2 - ethylamino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

14. 5 - [1 - Hydroxy - 2 - (2 - phenethylamino)butyl] - 8 - hydroxy - 3,4 - dihydrocarbostyril.

15. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)propyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

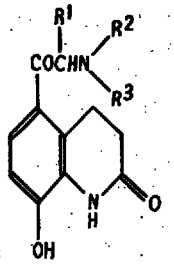
16. 5 - (1 - Hydroxy - 2 - morpholino)butyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

17. An acid addition salt of an 8 - hydroxycarbostyril derivative as claimed in any preceding Claim.

18. An acid addition salt according to Claim 17, which is a hydrochloride, a sulphate, a phosphate, a maleate, a fumarate or an oxalate.

19. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril 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 - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the following general formula (IIb):

* C L M S *



(IIb)

wherein R^1, R^2 and R^3 are as defined in any of Claims 1 to 7, or an acid addition salt thereof with hydrogen in the presence of a catalyst or with a reducing agent.

20. A process according to Claim 19, wherein the reduction is effected by using palladium black, palladium - on - carbon, platinum oxide or Raney nickel as a catalyst in an amount of from 0.05 to 1 mole per mole of said derivative of general formula (IIb) at a temperature of from room temperature to 150°C under a hydrogen atmosphere at a pressure of from atmospheric pressure to 100 atmospheres.

21. A process according to Claim 20, wherein the catalyst is used in an amount of from 0.1 to 0.5 mole per mole of said derivative of general formula (IIb).

22. A process according to Claim 20 or 21, wherein the temperature is from room temperature to 120°C.

23. A process according to any of Claims 20 to 22, wherein the pressure is from atmospheric to 50 atmospheres.

24. A process according to any of Claims 20 to 23, wherein the reduction is effected in the presence of water or methanol, ethanol or *iso* - propanol as a solvent.

25. A process according to Claim 19, wherein the reduction is effected by using lithium aluminium hydride or sodium borohydride as a reducing agent in an amount of from 2 to 10 moles per mole of said 5 - substituted - amino - acetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative at a temperature of from 0° to 100°C under atmospheric pressure.

26. A process according to Claim 25, wherein the reducing agent is used in an amount of from 2 to 5 moles per mole of said 5 - substituted - amino - acetyl - 8 - hydroxycarbostyril derivative.

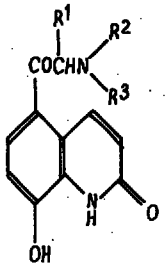
27. A process according to Claim 25 or 26, wherein the temperature is from 20° to 50°C.

28. A process according to any of Claims 25 to 26, wherein lithium aluminium hydride is employed as the reducing agent and the reduction is effected in the presence of anhydrous ethyl ether, ethyl acetate or tetrahydrofuran as a solvent.

29. A process according to any of Claims 25 to 26, wherein sodium borohydride is employed as the reducing agent and the reduction is effected in the presence of water or methanol, ethanol, *n* - propanol or *iso* - propanol as a solvent.

30. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril 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 12 to 15, 20 and 21.

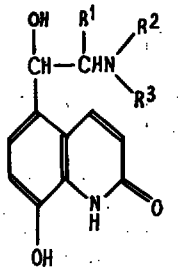
31. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in Claim 1, or an acid addition salt thereof, which comprises catalytically reducing with hydrogen a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - carbostyril derivative of the following general formula (VII):



(VII)

wherein R^1, R^2 and R^3 are as defined in Claim 1 or an acid addition salt thereof.

32. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in Claim 1, or an acid addition salt thereof which comprises catalytically reducing with hydrogen a 5 - (1 - hydroxy - 2 - substituted - aminoalkyl) - 8 - hydroxycarbostyril derivative of the following general formula (VIII):



(VIII)

whenever R^1, R^2 and R^3 are as defined in Claim 1, or an acid addition salt thereof.

33. A process according to Claim 31 or 32, wherein the catalyst is palladium black, platinum oxide, palladium - on - carbon, platinum black or Raney nickel.

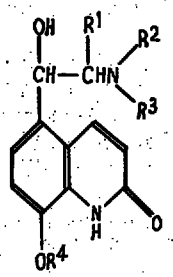
34. A process according to Claim 31 to 33, wherein the reduction is effected in water, methanol, ethanol or *iso* - propanol as a solvent.

* C L M S *

35. A process according to any of Claims 31 to 34, wherein the reaction is effected at a temperature of from room temperature to 150°C, in a hydrogen atmosphere at a pressure of from 1 to 100 atmospheres.

36. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril 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 16, 17 and 18.

37. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula I defined in Claim 1, which comprises dealkylating with a hydrogen halide a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative of the following general formula (IX):



(IX)

wherein R^1, R^2 and R^3 are as defined in Claim 1 and R^4 represents an alkyl group having from 1 to 4 carbon atoms.

38. A process according to Claim 37, wherein the hydrogen halide is hydrogen bromide, hydrogen chloride or hydrogen iodide.

39. A process according to Claim 37 or 38, wherein the hydrogen halide is employed as a solution thereof in methanol, ethanol, a propanol or water.

40. A process according to Claim 39, wherein an aqueous solution of the hydrogen halide at a concentration of from 10 to 50% is employed.

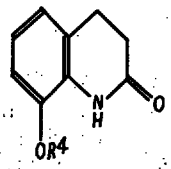
41. A process according to any of Claims 37 to 40, wherein an equimolar amount to a large excess of the hydrogen halide is employed with respect to the derivative of general formula (IX).

42. A process according to any of Claims 37 to 41, wherein the reaction is effected at from 100 to 150°C.

43. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in Claim 1, substantially as hereinbefore defined with reference to the foregoing Example 19.

44. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in any of Claims 1 to 7 which comprises the steps of:

(1) reacting a 8 - substituted - 3,4 - dihydrocarbostyril of the following general formula (VI):



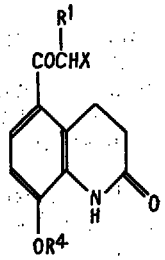
(VI)

wherein R^4 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, with an α - haloalkanoic acid of the following general formula (V):



(V)

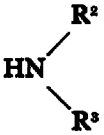
wherein R^1 is as defined above and X and X', which may be the same or different, each represents a halogen atom, in the presence or absence of a solvent and in the presence of a Lewis acid catalyst, to produce a corresponding 5 - (α - haloalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyril of the following general formula (IV):



(IV)

wherein R^1, R^4 and X are as defined above,

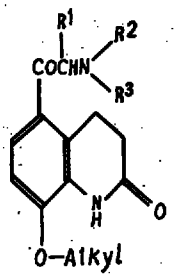
(2) reacting the resulting 5 - (α - haloalkanoyl) - 8 - substituted - 3,4 - dihydrocarbostyril of the formula (IV) with ammonia or an amine of the following general formula (III):



(III)

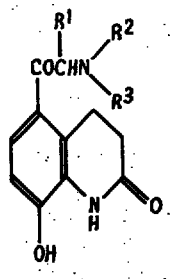
wherein R^2 and R^3 are as defined above, to produce a 5 - (α - substituted - amino-

alkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril of the following general formula (IIa):



(IIa)

wherein the term "Alkyl" means an alkyl group having 1 to 4 carbon atoms and R^1, R^2 and R^3 are as defined above, and/or a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the following general formula (IIb):



(IIb)

wherein R^1, R^2 and R^3 are as defined above, and dealkylating the derivative of the general formula (IIa) with a hydrogen halide to produce the 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the general formula (IIb), and

(3) reducing the resulting 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the general formula (IIb) with hydrogen in the presence of a hydrogenation catalyst or with a reducing agent.

45. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril of general formula (I) defined in Claim 1 or an acid addition salt thereof substantially as hereinbefore described.

46. A 5 - [1 - hydroxy - 2 - (substituted - amino)] - alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in Claim 1, or an acid addition salt thereof, when prepared by a process as claimed in any of Claims 14 to 45.

47. A pharmaceutical composition which comprises a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative as claimed in any of Claims 1 to 18 or 46 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

48. A pharmaceutical composition according to Claim 47 and in a formulation suitable for inhalation in the form of an aerosol spray.

49. A pharmaceutical composition according to Claim 47 and in tablet form.

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

51. A pharmaceutical composition according to Claim 47 and substantially as hereinbefore described.

52. A method of stimulating the activity of β - adreno - receptor, which comprises administering a pharmaceutically effective amount of a pharmaceutical composition as claimed in any of Claims 47 to 51.

53. A method of alleviating bronchial asthma which comprises administering a pharmaceutically effective amount of a pharmaceutical composition as claimed in any of Claims 47 to 51.

54. A method of alleviating bronchial asthma, according to Claim 53 and substantially as hereinbefore described with reference to the foregoing Reference Example.

55. An aerosol dispenser containing a pharmaceutical composition as claimed in Claim 48.

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