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PATENT SPECIFICATION (11) 1 496 770

(21) Application No. 55929/74 (22) Filed 27 Dec. 1974
(31) Convention Application No. 49/129381
(32) Filed 8 Nov. 1974
(31) Convention Application No. 49/129382
(32) Filed 8 Nov. 1974
(31) Convention Application No. 49/129383
(32) Filed 8 Nov. 1974
(31) Convention Application No. 49/129384
(32) Filed 8 Nov. 1974
(31) Convention Application No. 49/130726
(32) Filed 11 Nov. 1974
(31) Convention Application No. 49/130727
(32) Filed 11 Nov. 1974
(31) Convention Application No. 49/130729
(32) Filed 11 Nov. 1974 in
(33) Japan (JP)
(44) Complete Specification published 5 Jan. 1978
(51) INT CL² C07D 215/22 A61K 31/47
(52) Index at acceptance
C2C 1534 213 247 250 251 25Y 29X 29Y 30Y 322 32Y 351 352 360 362 364 365 36Y 620 623 624 625 633 650 652 672 761 762 790 79Y LK

(19)

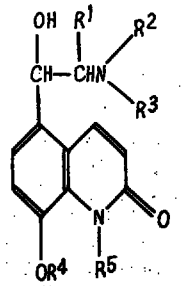
(54) 5-SUBSTITUTED ALKYL-8-SUBSTITUTED CARBOSTYRILS AND-3,4-DIHYDROCARBOSTYRIL DERIVATIVES AND PRODUCTION THEREOF

(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 carbostyril derivatives and to processes for preparing them.

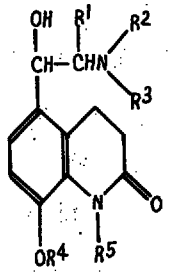
It is well known that certain carbostyril derivatives exhibit useful pharmaceutical activities. Representative compounds of this type have been disclosed in *Journal of Medical Chemistry*, Vol. 15, No. 3, pp, 260—266 (1972), Japanese Patent Publication No. 38789/1971 and *Chemical Abstracts, 62,* 16212e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

According to one aspect of the present invention there are provided 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivatives represented by the following general formula (Ia):



(Ia)

and 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivatives represented by the following general formula (Ib):

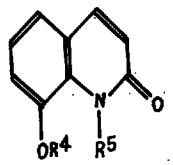


(Ib)

wherein R^1, R^4 and R^5 each represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, with at least one of R^4 and R^5 being an alkyl group, 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.

According to a further aspect of the present invention there is provided a process for preparing the derivatives represented by the foregoing formulae (Ia) and (Ib) and acid addition salts thereof, which comprises the steps of

(1) reacting an 8-substituted-carbostyril of the following general formula (VI):



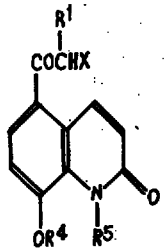
(VI)

wherein R^4 and R^5 are as defined above, with an α - haloalkanoic acid halide of the formula (V):



(V)

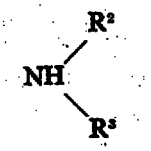
wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms; and X and X′, which may be the same or different, each represents a halogen atom, to obtain a 5 - (α - haloalkanoyl) - 8 - substituted - carbostyril derivative of the following general formula (IV):



(IV)

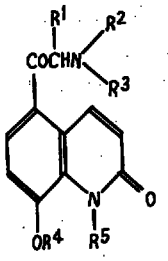
wherein R^1, R^4, R^5 and X are as defined above,

(2) reacting the resulting 5 - (α - haloalkanoyl) - 8 - substituted - carbostyril derivative 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 obtain a 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril derivative represented by the following general formula (II):



(II)

wherein R, R^1, R^2, R^3, R^4 and R^5 are as defined above, and

(3) reducing the resulting 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril derivative of the formula (II) by a catalytic reduction or a reduction using a reducing agent.

The 5 - [1 - hydroxy 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivatives of the formula (Ia) and 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,5 - dihydrocarbostyril derivatives of the formula (Ib) and the pharmaceutically acceptable acid addition salts thereof exhibit a β - adreno - receptor stimulating activity and, therefore, are useful as a bronchodilator, a peripheral vasodilator or an antihypertensive agent, particularly for use in the treatment of bronchial asthma.

The term "alkyl" as used herein in respect of R^1, R^2, R^3, R^4 and R^5 means a straight or branched chain alkyl group having 1 to 4 carbon atoms, and includes, for example, a methyl, ethyl, propyl, *iso* - propyl, *n* - 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" as used herein means heterocyclic groups containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms such as 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 term "halogen" as used herein comprises fluorine, chlorine, bromine and iodine, preferably, chlorine and bromine.

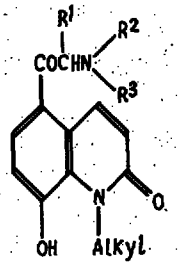
The compounds of the present invention represented by the formulae (Ia) and (Ib) can be prepared from a starting carbostyril compound of the formula (VI) according to the reaction schemes shown in the accompanying drawings in which:

Fig. 1 illustrates the preparation of the compounds of the formulae (Ia) and (Ib),

Fig. 2 illustrates the preparation of compounds of the formulae (Ia) and (Ib) wherein R^4 is a hydrogen atom and R^5 is an alkyl group and,

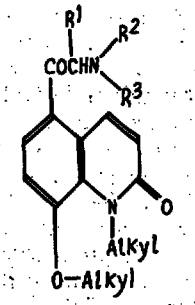
Fig. 3 illustrates the preparation of the compounds of the formulae (Ia) and (Ib) wherein R^4 is an alkyl group and R^5 is a hydrogen atom.

In Fig. 2, as a result of step (2) using a starting carbostyril of the formula (VI) wherein R^4 is a hydrogen atom or an alkyl group and R^5 is an alkyl group, there is produced either a 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril derivative of the following general formula (IIa):



(IIa)

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



(IIb)

wherein each term "Alkyl" represents an alkyl group having 1 to 4 carbon atoms as defined for R^4 and R^1, R^2 and R^3 are as defined above. Subsequent dealkylation of the alkyl group at the 8 - position of the 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril of the formula (IIb) with a hydrogen halide produces the corresponding 8 - hydroxycarbostyril having the formula (IIa) which can be reduced in accordance with the procedures described for the reduction of the 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril derivative of the formula (II) to produce the 8 - hydroxy - substituted - carbostyril derivatives of the formulae (Ia) and (Ib).

The 1- and/or 8-substituted-carbostyril (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 - haloalkanoic acid halide of the formula (V) which can be used in this invention includes chloroacetyl chloride, α - chloropropionyl chloride, α - bromopropionyl chloride, α - chlorobutyryl chloride, α - bromobutyryl chloride, α - bromobutyryl bromide and α - chlorovaleryl chloride.

The reaction between the carbostyril compound of the formula (VI) and the α - haloalkanoic acid halide of the formula (V) may be conducted using a Lewis acid as a catalyst, for example, aluminium chloride, aluminium bromide, zinc chloride, ferric chloride, stannic chloride, boron trifluoride, in an amount of from 2 to 10 moles, preferably from 3 to 6 moles, per mole of the starting carbostyril (VI). The α - haloalkanoic acid halide of the formula (V) is used in from an equimolar amount to a large excess relative to the carbostyril of the formula (VI) but generally in an amount of from 2 to 20 moles, most preferably 2 to 10 moles, per mole of the starting carbostyril of the formula (VI). The reaction may be carried out in the absence or presence of an appropriate solvent such as carbon disulphide, nitrobenzene, diethyl ether or dioxane and in the presence of the above enumerated catalyst, advantageously under anhydrous conditions, at from room temperature (about 20 to 30°C) to 150°C, preferably from room temperature to 80°C for a period of from 1 to 20 hours, preferably from 4 to 10 hours. A solvent is usually used in a volume of from 0.5 to 20, preferably from 2 to 10 times, the volume of the reactants.

The amines of the formula (III) which can be used in the reaction with the 5 - (α - haloalkanoyl) - 1- and/or -8 - substituted carbostyril of the formula (IV) include alkylamines, for example, methylamine, ethylamine, *n* - propylamine, *iso* - propylamine, *n* - butylamine, *sec* - butylamine, *tert* - butylamine; cyclopentylamine, cyclohexylamine; aralkylamine, for example, benzylamine, α - methylbenzylamine, α,α - dimethylbenzylamine, phenethylamine, or α,α - dimethylphenethylamine; and substituted or unsubstituted heterocyclic amines, for example,

pyrrolidine, piperidine, morpholine, piperazine, 2 - methylpiperidine, 3 - methylpiperidine or N - methylpiperazine.

This reaction between the amine (or ammonia) of the formula (III) and the 5 - (α - haloalkanoyl) - 1- and/or -8 - substituted - carbostyril of the formula (IV) may be effected in the absence of a solvent since the amine reactant itself also serves as a solvent, but it is advantageous to conduct the reaction in an appropriate solvent. Suitable examples of solvents 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 preferred.

This reaction may be effected using from an equimolar amount to, especially in the absence of a solvent, a large excess of the ammonia or the amine of the formula (III), preferably from 2 to 10 moles of the amine per mole of the 5 - (α - haloalkanoyl) - 1- and/or -8 - substituted - carbostyril or the formula (IV) at from atmospheric pressure to 10 atmospheres 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, in an appropriate solvent or using the amine of the formula (III) *per se* as a solvent to obtain a 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy - carbostyril of the formula (VIIa), a 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril of the formula (IIa) or a 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril of the formula (IIb).

Thus, when the 8 - hydroxycarbostyril of the formula (VI) wherein R^4 is a hydrogen atom (R^5 being alkyl) is used as a starting material, the 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxycarbostyril of the formula (IIa) is obtained, which can be subjected to a subsequent reduction reaction to produce the 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (Ib).

When the 8 - alkoxycarbostyril of the formula (VI) wherein R^4 is an alkyl group (R^5 being a hydrogen atom) is used as a starting material, the corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril of the formula (VIIa) (see Fig. 3) is obtained. This may then be reduced as described hereinafter.

When the 8 - alkoxycarbostyril of the formula (VI) wherein R^4 is an alkyl group (R^5 also being alkyl) is used as a starting material, the corresponding 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril of the formula (IIb) is obtained. The resulting 1 - alkyl - 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril (IIb) is then reacted with a hydrogen halide to dealkylate the 8-position of the carbostyril moiety thereby obtaining the compound of the formula (IIa) which can be subjected to the subsequent reduction described above to produce a compound of the formula (Ib).

The hydrogen halides used in this dealkylation of the alkoxy group at the 8-position include, for example, hydrogen bromide, hydrogen chloride and hydrogen iodide, preferably, hydrogen bromide. These hydrogen halides can advantageously be employed in an appropriate solvent such as methanol, ethanol, a propanol or, 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 of the alkoxy group at the 8 - position 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 (IIb) by heating to a temperature of from about 100° to about 150°C, preferably at the refluxing temperature, for about 1 to 10 hours, preferably 3 to 8 hours.

The reduction of the 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril of the formula (II) to the compounds of the present invention represented by the formula (Ia) can be conducted by a conventional reduction using a reducing agent such as lithium aluminium hydride or sodium borohydride, or a conventional catalytic reduction in the presence of a catalyst such as palladium black, palladium-on-carbon, Raney nickel, platinum black or platinum oxide, and hydrogen.

The above 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 (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 a reducing agent, the solvent is preferably water or an alcohol such as methanol or ethanol, and when lithium aluminium hydride is used as a 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 using the above catalyst in an amount of from 0.05 to 1 mole, preferably from 0.1 to 0.5 moles, per mole of the carbostyril 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.

In the above catalytic reduction, 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril of the formula (II) is first reduced to the compound of the formula (Ia) and then ultimately reduced to the compound of the formula (Ib), i.e., a 3,4 - dihydrocarbostyril compound.

The conversion of the compound of the formula (Ia) to the compound of the formula (Ib) or *vice versa* can be carried out conveniently by a conventional hydrogenation or dehydrogenation, respectively, as is well known in the art.

The conversion of the compound of the formula (Ia) to the compound of the formula (Ib), i.e., hydrogenation, may be conducted in the same manner as described for the catalytic reduction of the compound of the formula (II) with hydrogen in the presence of a hydrogenation catalyst.

The conversion of the compound of the formula (Ib) to the compound of the formula (Ia), i.e., dehydrogenation, may be conducted by any procedure which is capable of removing a hydrogen atom from each of the 3- and 4-positions of the carbostyril moiety to form a double bond between the 3- and 4-positions. This dehydrogenation may be attained by (1) a procedure using a dehydrogenating agent, for example, chloranil(tetrachloro - 1,4 - benzoquinone) or dichlorodicyano - 1,4 - benzoquinone; (2) a procedure using a dehydrogenating metal catalyst such as palladium black, platinum black, Raney nickel or platinum oxide; or (3) a procedure using a dehydrogenating agent such as selenium dioxide or sulphur. Advantageously the above procedure (1) or (2) is used. Either of the hydrogenation and the dehydrogenation may be carried out in a solvent such as aromatic hydrocarbons, for example, benzene, toluene, xylene, phenetol or chlorobenzene; lower alcohols, for example, methanol, ethanol, *iso* - propanol or *tert* - butanol; ethers, for example, dioxane; ketones, for example, acetone; water; or acetic acid. The dehydrogenation is advantageously carried out at a temperature of from room temperature to the refluxing temperature of the dehydrogenation system, preferably at or near the refluxing temperature.

The compounds of the present invention having the formulae (Ia) and (Ib) wherein R^4 represents an alkyl group and R^5 represents a hydrogen atom can also be prepared by the procedures illustrated in Fig. 3 of the accompanying drawings.

The carbostyril compounds of the formula (Ia) having an alkoxy group at the 8-position and a hydrogen atom at the 5-position can be prepared from the corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxycarbostyril of the formula (VIIa) by reduction with a reducing agent in the same manner as described previously for the reduction of the compound of the formula (II) shown in Fig. 1. Also, the compound of the formula (Ia) having an alkoxy group at the 8-position and a hydrogen atom at the 5-position can also be prepared from the corresponding 8-hydroxy compound of the formula (VIIIa) by alkylation.

The alkylation of the compounds of the formulae (VIIIa) and (VIIIb) may be carried out by reacting them with an alkylating agent as is well known in the art in the presence of a basic compound. Suitable examples of alkylating agent are alkyl halides such as alkyl iodides, alkyl chlorides and alkyl bromides, dialkylsulphates such as dimethyl sulphate and diethyl sulphate, etc. Suitable examples of the basic compounds are alkali metals such as sodium metal, potassium metal and their hydrixides, carbonates, bicarbonates and alcoholates and aromatic amines such as pyridines and piperidine.

The alkylation proceeds advantageously in a solvent such as water, lower alcohols such as methanol, ethanol, *iso* - propanol, *n* - butanol, or ketones such as acetone or methyl ethyl ketone, using the alkylating agent in an amount of from an equimolar to a large excess of the alkylating agent, preferably from 5 to 10 moles, per mole of the compound of the formula (VIIIa) or (VIIIb). The alkylation generally proceeds at room temperature.

Further, the 3,4 - dihydrocarbostyril compounds of the formula (Ib) having an alkoxy group at the 8-position and a hydrogen atom at the 5-position can be prepared from the corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (VIIb) by reduction in the same manner as described previously for the reduction of the compound of the formula (II) and either a catalytic reduction with hydrogen or a reduction with the reducing agent can be employed. Also, the compound of the formula (Ia) having an alkoxy group at the 8-position and a hydrogen atom at the 5-position can be prepared from the corresponding 8 - hydroxy compound of the formula (VIIIb) by alkylation in the same manner as described for the alkylation of the compound of the formula (VIIIa).

Alternatively, the compound of the formula (Ib) having an alkoxy group at the 8-position and a hydrogen atom at the 5-position can be prepared from the corresponding 5 - (α - substituted - aminoalkanoyl) - 8 - alkoxy-

carbostyril of the formula (VIIa) by reduction. This reduction can be carried out by the catalytic reduction with hydrogen as described for the preparation of the compound of the formula (Ib) from the compound of the formula (Ia) shown in Reaction Scheme I.

The starting materials of the formulae (VIIa), (VIIb), (VIIIa) and (VIIIb) employed in the processes illustrated in Fig. 3, can also be prepared in accordance with the processes described for the preparation of the compounds of formulae (Ia), (Ib), (IIa) and (IIb) using 8 - hydroxy or 8 - alkoxycarbostyril derivatives.

The compounds of general formula (VIIa) fall within the general formula (II) defined hereinbefore.

The compounds of general formula (VIIb) wherein R^1 represents a hydrogen atom and a process for their preparation are described and claimed in our copending Patent Application No. 28862/77 (Serial No. 1,496,873) of even date.

The compounds of general formula (VIIb) wherein R^1 represents an alkyl group having from 1 to 4 carbon atoms and a process for their preparation are described and claimed in our copending Patent Application No. 28864/77 (Serial No. 1,496,875) of even date.

The compounds of general formula (VIIIa) wherein R^1 represents a hydrogen atom and a process for their preparation are described and claimed in our copending Patent Application No. 5590/74 (Serial No. 1,496,769) of even date.

The compounds of general formula (VIIIa) wherein R^1 represents an alkyl group and a process for their preparation are described and claimed in our copending Patent Application No. 55897/74 (Serial No. 1,496,766) of even date.

The compounds of general formula (VIIIb) wherein R^1 represents an alkyl group having 1 to 4 carbon atoms 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 compounds of formula (II) form the subject of our copending Patent Application No. 29523/77 (Serial No. 1,496,871) of even date.

Both the compounds of the formula (Ia) and the compounds of the formula (Ib) 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 or hydrobromic acid, or organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid or ascorbic acid. These acid addition salts may 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 formula (Ia) or (Ib) dissolved in an appropriate organic solvent such as methanol, ethanol, *iso* - propanol or acetone.

Both the free bases of the compounds (Ia) and (Ib) and 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 of the present invention contain two asymmetrical centres and, therefore, can be present in four optically active forms.

Particularly preferred compounds of the formulae (Ia) and (Ib) are the following basic compounds and their hydrochlorides, sulphates, phosphates, maleates, fumarates and oxalates:

1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril.
1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.
5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - methoxycarbostyril.
5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril.

The present invention is further illustrated by the following Examples. Unless otherwise indicated, all parts, percentages, ratios and the like are by weight.

EXAMPLE 1

30 Millilitres of nitrobenzene and 70 ml of chloroacetyl chloride (V) were added to 40 g of 1 - methyl - 8 - methoxycarbostyril (VI), and 130 g of aluminium chloride were added slowly to the mixture while cooling with ice-water. The mixture was allowed to react at a temperature of 60°C for 4 hours while stirring. The reaction mixture was then poured into one litre of ice-water to precipitate the product. The precipitate was filtered, washed with diethyl ether and recrystallized from a mixture of chloroform and ethanol (2:5 by volume) to obtain 32 g of white amorphous 1 - methyl - 5 - chloroacetyl - 8 - methoxycarbostyril (IV) having a melting point of 204 to 205.5°C. The identity of the product thus obtained was confirmed by elemental analysis and IR and NMR spectral analyses.

EXAMPLE 2

40 Millilitres of nitrobenzene and 12 ml of chloroacetyl chloride (V) were added to 7.4 g of 1 - methyl - 8 - hydroxycarbostyril (VI), and 20 g of aluminium chloride were

added slowly to the mixture while cooling with ice-water. The mixture was allowed to react at a temperature of 60°C for 18 hours while stirring. The reaction mixture was then poured into 500 ml of ice-water to precipitate the product. The precipitate was filtered, washed with diethyl ether and recrystallized from a mixture of ethanol and dimethylformamide (1:1 by volume) to obtain 2.8 g of white amorphous 1 - methyl - 5 - chloroacetyl - 8 - hydroxycarbostyril (IV) having a melting point of 287 to 289°C (with decomposition). The identity of the product thus-obtained was confirmed by elemental analysis and IR and NMR spectral analyses.

EXAMPLE 3

2.7 Grams of 1 - methyl - 5 - chloroacetyl - 8 - methoxycarbostyril (IV) prepared as described in Example 1 were dissolved in 40 ml of *iso* - propanol, and 9 g of *iso* - propylamine (III) were added to the solution while heating the solution at a temperature of 55 to 60°C over a period of 1.5 hours. After completion of the addition, the mixture was allowed to react for one hour while stirring. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in 40 ml of *iso*-propanol. The solution was then filtered to remove any insoluble material, and the filtrate was adjusted to a pH of 2—3 with concentrated hydrochloric acid. The mixture was cooled with ice and the precipitate formed was filtered and recrystallized from ethanol to obtain 0.4 g of white amorphous 1 - methyl - 5 - *iso* - propylaminoacetyl - 8 - methoxycarbostyril (IIb) hydrochloride. The identity of the product thus obtained was confirmed by elemental analysis and IR spectral analysis.

EXAMPLE 4

10 Millilitres of *iso* - propanolamine (III) were added to 1.6 g of 1 - methyl - 5 - chloroacetyl - 8 - hydroxycarbostyril (IV) prepared as described in Example 2, and the mixture was allowed to react at a temperature of 35°C for 2 hours while stirring. The reaction mixture was concentrated under reduced pressure, and the residue was distilled azeotropically with ethanol to dryness. The resulting residue was dissolved in 20 ml of ethanol, and the solution was filtered to recover the insoluble material which was then dissolved in hot ethanol. The solution was adjusted to a pH of 2—3 with concentrated hydrochloric acid and cooled with ice. The precipitate formed was filtered and dissolved in 20 ml of water. The solution was adjusted to a pH of 6.5 to 7.5 with sodium bicarbonate and the precipitate formed was filtered and recrystallized from ethanol to obtain 1.1 g of white amorphous 1 - methyl - 5 - *iso* - propylaminoacetyl - 8 - hydroxycarbostyril (IIa) having a melting point of 136 to 138°C (with decomposition).

EXAMPLE 5

2.0 Grams of 1 - methyl - 5 - *iso* - propylaminoacetyl - 8 - methoxy - carbostyril (IIb) hydrochloride prepared as described in Example 3 were dissolved in 30 ml of a 47% aqueous solution of hydrobromic acid, and the solution was heated in an oil bath at a temperature of 120 to 130°C for 8 hours under refluxing. 10 ml of water was then added to the reaction mixture which was then concentrated by distillation. 10 Ml of water was again added to the mixture followed by concentration. After allowing the mixture to cool, the precipitate formed was filtered and dissolved in 60 ml of water by heating. The resulting solution was adjusted to a pH of 6.5 to 7.5 with sodium bicarbonate and the precipitate formed was filtered. Recrystallization of the precipitate from ethanol yielded 0.45 g of white amorphous 1 - methyl - 5 - *iso* - propylaminoacetyl - 8 - hydroxycarbostyril (IIa) having a melting point of 136 to 138°C (with decomposition). The identity of the product thus obtained was confirmed by elemental analysis and IR and NMR spectral analyses.

EXAMPLE 6

0.45 Gram of 1 - methyl - 5 - isopropylaminoacetyl - 8 - hydroxycarbostyril (IIa) was dissolved in 50 ml of methanol, and 0.2 g of sodium borohydride was added slowly to the solution while ice-cooling and stirring. The stirring was further continued for an additional hour and the resulting reaction mixture was adjusted to a pH of 2 to 3 with concentrated hydrochloric acid. The precipitate formed was then removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 20 ml of ethanol. The solution was filtered to remove any insoluble material. The filtrate was concentrated under reduced pressure and 20 ml of ethanol was added thereto. The mixture was then filtered to remove any insoluble material. The filtrate was concentrated under reduced pressure to dryness and 40 ml of ethanol was added to the residue to remove any ethanol-soluble material remaining in the residue. The ethanol-insoluble material was washed twice with 20 ml portions of cold water and recrystallized from ethanol to obtain 0.3 g of white amorphous 1 - methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril (Ia) hydrochloride having a melting point of 202 to 203.5°C (with decomposition). The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 7

1 Gram of 1 - methyl - 5 - *iso* - propylaminoacetyl - 8 - hydroxycarbostyril (IIa) hydrochloride was suspended in 100 ml of water, and 0.1 g of palladium black and 0.1 g of palladium-on-carbon were added to the suspension. The mixture was catalytically reduced with hydrogen at atmospheric pressure at a temperature of 60 to 70°C for 25 hours. After completion of the reduction, the reaction mixture was filtered, and the filtrate was concentrated to dryness under reduced pressure. The resulting residue was crystallized from acetone and then recrystallized from ethanol to obtain 0.3 g of white amorphous 1 - methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (Ib) having a melting point of 196 to 197°C (with decomposition). The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 8

1.0 Gram of 5 - *iso* - propylaminoacetyl - 8 - methoxycarbostyril (IIb) was dissolved in 50 ml of methanol, and 0.6 g of sodium borohydride was added slowly to the solution while ice-cooling and stirring. The mixture was then stirred at room temperature for one hour. The reaction mixture was adjusted to a pH of 2 to 3 with concentrated hydrochloric acid, and the precipitate formed was filtered. The filtrate was concentrated to dryness and crystallized from acetone. Recrystallization of the product from ethanol yielded 0.8 g of a material having a melting point of 230 to 231°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)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril (Ib) hydrochloride monohydrate.

EXAMPLE 9

2 Grams of 5 - *iso* - propylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (VIIb) were dissolved in 70 ml of methanol, and 1 g of sodium borohydride was added slowly to the solution while cooling with ice-water. The mixture was then stirred at room temperature for an additional hour. The reaction mixture was adjusted to a pH of 1 with concentrated hydrochloric acid, and the precipitate formed was filtered. The filtrate was concentrated to dryness and the resulting residue was recrystallized from ethanol to obtain 1.5 g of a material having a melting point of 206 to 208°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)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril (Ib) hydrochloride.

EXAMPLE 10

3 Grams of 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril (VIIIa) hydrochloride were dissolved in 20 ml of water, and 0.9 g of sodium hydroxide was added to the solution. 1.3 Grams of dimethyl sulphate were then added dropwise to the solution while ice-cooling and stirring over a period of one hour. The mixture was stirred for 2 hours at a temperature of 40 to 50°C, and the reaction mixture was extracted with chloroform. The chloroform extract was washed with water and dried, and hydrogen chloride gas was introduced into the chloroform extract. The precipitated crystals were recrystallized from a mixture of ethanol and acetone to obtain 2.3 g of a material having a melting point of 235 to 237°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)ethyl - 8 - methoxycarbostyril (Ia) hydrochloride monohydrate.

EXAMPLE 11

2.6 Grams of 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (VIIIb) were dissolved in 30 ml of water and 0.45 g of sodium hydroxide was added to the solution. 1.3 g of dimethyl sulphate were then added dropwise to the solution while ice-cooling and stirring over a period of one hour. The reaction mixture was stirred for 2 hours at a temperature of 40 to 50°C and extracted with chloroform. The chloroform extract was washed with water and dried, and hydrogen chloride gas was introduced into the chloroform extract. The precipitated crystals were recrystallized from ethanol to obtain 2.2 g of a material having a melting point of 206 to 208°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)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril hydrochloride (Ib).

EXAMPLE 12

10 Millilitres of a 47% aqueous hydrobromic acid was added to 1 g of 1 - methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)-ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril (VIIb) hydrochloride monohydrate, and the mixture was heated under refluxing for 15 hours, then concentrated to dryness. Acetone was added to the resulting residue to crystallize the product which was then adjusted to a pH of 8 with a dilute aqueous sodium hydroxide solution. The precipitated crystals were filtered, washed with water and dissolved in ethanol. The solution was adjusted to a pH 1 with concentrated hydrochloric acid and concentrated 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 198 to 200°C (with decomposition). The identity of the product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 1 - methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)-ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (Ib) hydrochloride.

REFERENCE EXAMPLE

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

Male hydrid 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 an der Bronchial 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 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 I below was then administered to each of the anaesthetized dogs through the femoral vein at the various dosage levels shown in Table I below, 1 minute before the administration of the histamine. Sodium pentocarbital 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 I below.

TABLE I

Bronchial Resistance (%)

Compound	Dosage Level (μg/Kg)								
	0.01	0.03	0.1	0.3	1.0	3.0	10	30	100
1-Methyl-5-(1-hydroxy-2-*iso*-propylamino)-ethyl-8-hydroxycarbostyril Hydrochloride	0	0	0	5.2	16.8	36.5	—	—	—
5-(1-Hydroxy-2-*iso*-propylamino)-ethyl-8-methoxycarbostyril Hydrochloride Monohydrate	0	0	0	0	8.2	17.9	—	—	—
(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

Further, the acute toxicity was determined in respect of the test compounds shown in Table II below 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 Isoproterenol were used as controls. The LD_{50} (50% lethal dose) results are as follows:

TABLE II

Compound	LD_{50} (mg/Kg) i.v.	p.o.
1-Methyl-5-(1-hydroxy-2-*iso*-propylamino)-ethyl-8-hydroxycarbostyril Hydrochloride	46.5 (40.1–51.8)	750 (523–1147)
5-(1-Hydroxy-2-*iso*-propylamino)ethyl-8-methoxycarbostyril Hydrochloride	86.3 (65.3–103.7)	830 (473–1371)
Salbutamol	57.1 (52.7–61.9)	4620* (4160–5130)*
		660 (412.5–1056)
Isoproterenol	112.5 (87.9–144.0)	2587*
		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, inhalent (aerosol spray) or a 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 together with pharmaceutical carriers or diluents such as commonly employed in conventional pharmaceutical compositions. The compositions 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. A soluble tablet which is suitable for sublingual administration, i.e., troche or lozenge, can 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 the well-established pharmaceutical techniques.

Formulation 1

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

Components	Amount
1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril	1 mg
Corn Starch	70 mg
Magnesium stearate	9 mg
Lactose	20 mg
Total	100 mg

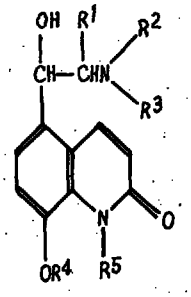
Formulation 2

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

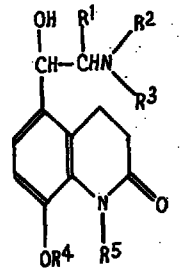
Components	Amount
1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril	50 mcg
Oleic Acid	10 mcg
Dichlorodifluoromethane	57 mg
Trichlorofluoromethane	25 mg

WHAT WE CLAIM IS:—

1. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril or 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative represented by the formula (Ia) or (Ib):



(Ia)



(Ib)

wherein R^1, R^4 and R^5, which may be the same or different, each represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, with at least one of R^4 and R^5 being an alkyl group, 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^1 and R^2 each represents a hydrogen atom and R^3 represents a methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, *sec* - butyl or *tert* - butyl group.

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

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

5. A derivative according to Claim 1, wherein R^1 and R^2, 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.

6. 1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyril.

7. 1 - Methyl - 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

8. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - methoxycarbostyril.

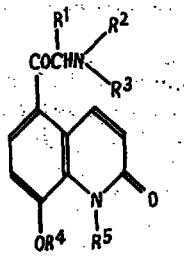
9. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril.

10. An acid addition salt of a derivative as claimed in any preceding Claim.

11. An acid addition salt according to Claim 9, which is a hydrochloride, a sulphate, a phosphate, a maleate, a fumarate or an oxalate.

12. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in any of Claims 1 to 5 or an acid addition salt thereof, which comprises reducing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril of the general formula (Ia) defined in any of Claims 1 to 5 or an acid addition salt thereof, with hydrogen in the presence of a catalyst or with a reducing agent.

13. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (Ib) defined in any of Claims 1 to 5, or an acid addition salt thereof which comprises reducing a 5 - (α - substituted - aminoalkanoyl) 8 - substituted carbostyril derivative of the following general formula (II):



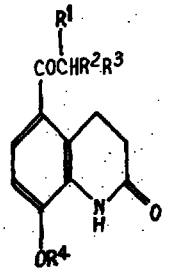
(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in any of Claims 1 to 5, or an acid addition salt thereof, with hydrogen in the presence of a catalyst or with a reducing agent.

14. A process for producing a 5 - (1 - hydroxy - substituted - aminoalkanoyl) - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in any of Claims 1 to 5, wherein R^5 represents a hydrogen atom and R^4 represents an alkyl group having from 1 to 4 carbon atoms, which comprises reducing a 5 - (α - substituted - aminoalkanoyl) 8 - alkoxy - 3,4 -

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dihydrocarbostyril of the following general formula (VIIb):



(VIIb)

wherein R^1, R^2, R^3 and R^4 are as defined in any of Claims 1 to 5, with hydrogen in the presence of a catalyst or with a reducing agent.

15. A process according to Claim 12, 13 or 14, 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 the derivative of general formula (Ia), (II) or (VIIb) at a temperature of from room temperature to 150°C under a hydrogen atmosphere at a pressure of from atmospheric pressure to 100 atmospheres.

16. A process according to Claim 15, wherein the catalyst is used in an amount of from 0.1 to 0.5 mole per mole of the derivative of general formula (Ia), (II) or (VIIb).

17. A process according to Claim 15 or 16, wherein the temperature is from room temperature to 120°C.

18. A process according to any of Claims 15 to 17, wherein the pressure is from atmospheric to 50 atmospheres.

19. A process according to any of Claims 15 to 18, wherein the reduction is effected in the presence of water or methanol ethanol or *iso* - propanol as a solvent.

20. A process according to Claim 12, 13 or 14, wherein the reduction is effected by using lithium aluminium hydride or sodium borohydride as a reducing agent in an amount of from about 2 to 10 moles per mole of the derivative of general formula (Ia), (II) or (VIIb) at a temperature of from 0° to 100°C under atmospheric pressure.

21. A process according to Claim 20, wherein the reducing agent is used in an amount of from 2 to 5 moles per mole of the derivative of general formula (Ia), (II) or (VIIb).

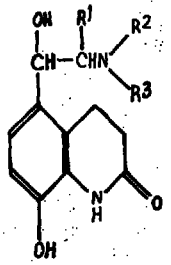
22. A process according to Claim 20 or 21, wherein the temperature is from 20° to 50°C.

23. A process according to any of Claims 20 to 22, 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.

24. A process according to any of Claims 20 to 23, 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.

25. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in Claim 1, or an acid addition salt thereof, substantially as hereinbefore described with reference to any one of the foregoing Examples 8, 9, 11 and 12.

26. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in any of Claims 1 to 5, wherein R^4 represents an alkyl group having from 1 to 4 carbon atoms and R^5 represents a hydrogen atom, which comprises alkylating a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - 3,4 - dihydrocarbostyril of the following general formula (VIIIb):



(VIII b)

wherein R^1, R^2 and R^3 are as defined in any of claims 1 to 5.

27. A process according to Claim 26, wherein the alkylation is effected in the presence of sodium metal, potassium metal, a hydroxide, carbonate, bicarbonate or alcoholate of sodium or potassium or pyridine or piperidine as a basic substance.

28. A process according to Claim 26 or 27, wherein there is employed as an alkylating agent an alkyl iodide, alkyl chloride, alkyl bromide or dialkyl sulphate.

29. A process according to any of Claims 26 to 28, wherein there is employed from an equimolar amount to a large excess of alkylating agent with respect to the 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (VIIIb).

30. A process according to Claim 29, wherein the amount of alkylating agent is from 5 to 10 moles per mole of the derivative of general formula (VIIIb).

31. A process according to any of Claims 26 to 30, wherein the alkylation is effected in water, a lower alcohol or a ketone as a solvent.

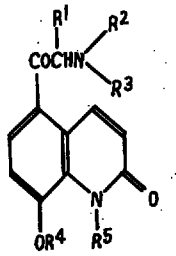
32. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (Ib) defined in Claim 1, wherein R^4 represents an alkyl group hav-

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ing from 1 to 4 carbon atoms and R^5 represents a hydrogen atom, substantially as hereinbefore described with reference to the foregoing Example 11.

33. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (Ib) defined in Claim 1, or an acid addition salt thereof, when prepared by a process as claimed in any of Claims 12 to 32.

34. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivative of the general formula (Ia) defined in any of Claims 1 to 5, or an acid addition salt thereof which comprises reducing a 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - carbostyril derivative of the following general formula (II):



(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in any of Claims 1 to 5, or an acid addition salt thereof, with hydrogen in the presence of a catalyst or with a reducing agent.

35. A process according to Claim 34, 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 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative at a temperature of from room temperature to 150°C under a hydrogen atmosphere at a pressure of from atmospheric pressure to 100 atmospheres.

36. A process according to Claim 35, wherein the catalyst is used in an amount of from 0.1 to 0.5 mole per mole of said 5 - (α - substituted - aminoalkanoyl - 8 - substituted carbostyril derivative.

37. A process according to Claim 35 or 36, wherein the temperature is from room temperature to 120°C.

38. A process according to any of Claims 35 to 37, wherein the pressure is from atmospheric to 50 atmospheres.

39. A process according to any of Claims 35 to 38, wherein the reduction is effected in the presence of water or methanol ethanol or *iso* - propanol as a solvent.

40. A process according to Claim 34, wherein the reduction is effected by using lithium aluminium hydride or sodium borohydride as a reducing agent in an amount of from about 2 to 10 moles per mole of said 5 - substituted aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative at a temperature of from 0° to 100°C under atmospheric pressure.

41. A process according to Claim 40, 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.

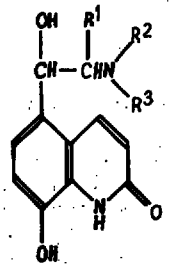
42. A process according to Claim 40 or 41, wherein the temperature is from 20° to 50°C.

43. A process according to any of Claims 40 to 42, 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.

44. A process according to any of Claims 40 to 43, 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.

45. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril of the general formula (Ia) defined in Claim 1, or an acid addition salt thereof, substantially as hereinbefore described with reference to the foregoing Examples 6 or 10.

46. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril of the general formula (Ia) defined in any of Claims 1 to 5, wherein R^4 represents an alkyl group having from 1 to 4 carbon atoms and R^5 represents a hydrogen atom which comprises alkylating a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - hydroxy - carbostyril of the following general formula (VIIIa):



(VIIIa)

wherein R^1, R^2 and R^3 are as defined in any of Claims 1 to 5.

47. A process according to Claim 46, wherein the alkylation is effected in the presence of sodium metal, potassium metal, a hydroxide, carbonate, bicarbonate or alcoholate or sodium or potassium or pyridine or piperidine as a basic substance.

48. A process according to Claim 46 or 47, wherein there is employed as an alkylat-

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ing agent an alkyl iodide, alkyl chloride, alkyl bromide or dialkyl sulphate.

49. A process according to Claims 46 to 48, wherein there is employed from an equimolar amount to a large excess of alkylating agent with respect to the derivative of the general formula (VIIIa).

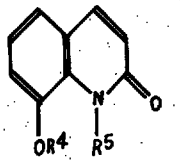
50. A process according to Claim 49, wherein the amount of alkylating agent is from 5 to 10 moles per mole of the derivative of general formula (VIIIa).

51. A process according to Claims 46 to 50, wherein the alkylation is effected in water, a lower alcohol or a ketone as a solvent.

52. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivative of the general formula (Ia) defined in Claim 1, wherein R^4 represents an alkyl group having from 1 to 4 carbon atoms and R^5 represents a hydrogen atom, substantially as hereinbefore described with reference to the foregoing Example 10.

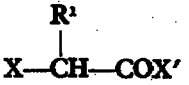
53. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril or 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ia) or (Ib) defined in any of Claims 1 to 5, which comprises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

(1) reacting an 8 - substituted - carbostyril of the following general formula (VI):



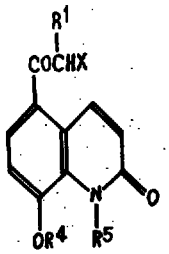
(VI)

wherein R^4 and R^5 are as defined in any of Claims 1 to 5, with an α - haloalkanoic acid halide of the following general formula (V):



(V)

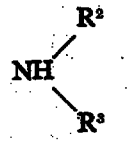
wherein R^1 is as defined in any of Claims 1 to 5, and X and X', which may be the same or different, each represents a halogen atom, to obtain a 5 - (α - haloalkanoyl) - 8 - substituted - carbostyril derivative having the following general formula (IV):



(IV)

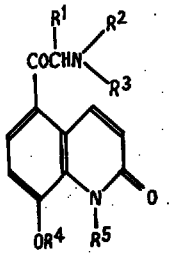
wherein R^1, R^4, R^5 and X are as defined in any of Claims 1 to 5,

(2) reacting the resulting 5 - (α - haloalkanoyl) - 8 - substituted - carbostyril derivative of the general formula (IV) with an amine of the following general formula (III):



(III)

wherein R^2 and R^3 are as defined in any of Claims 1 to 5, to obtain a 5 - (α - substituted - aminoalkanoyl) - 8 - substituted - 3,4 - carbostyril derivative represented by the following general formula (II):



(II)

wherein R, R^1, R^2, R^3, R^4 and R^5 are as defined in any of Claims 1 to 5, and

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

54. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril or 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ia) or (Ib) defined in Claim 1, substantially as hereinbefore described.

55. A 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivative of the general formula (Ia) defined in Claim 1, or a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in Claim 1, or an acid addition salt thereof, when prepared by a process as claimed in any of Claims 12 to 54.

56. A pharmaceutical composition which comprises a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril or 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivative as claimed in any of Claims 1 to 11 or 55, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

57. A pharmaceutical composition accord-

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ing to Claim 56 and in a formulation suitable for inhalation in the form of an aerosol spray.

58. A pharmaceutical composition according to Claim 56 and in tablet form.

59. A pharmaceutical composition substantially as hereinbefore described with reference to the foregoing Formulations 1 or 2.

60. A pharmaceutical composition according to Claim 56 and substantially as hereinbefore described.

61. 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 56 to 60.

62. 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 56 to 60.

63. A method of alleviating bronchial asthma in a non-human mammal, according to Claim 62 and substantially as hereinbefore described with reference to the foregoing Reference Example.

64. An aerosol dispenser containing a pharmaceutical composition as claimed in Claim 57.

65. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - carbostyril derivative of the general formula (Ia) which comprises dehydrogenating a 5 - [1 - hydroxy - 2 - (substituted - amino)]alkyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (Ib) defined in Claim 1.

GEE & CO.,
Chartered Patent Agents,
Chancery House,
Chancery Lane,
London WC2A 1QU,
and
39 Epsom Road,
Guildford, Surrey,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1978
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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