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

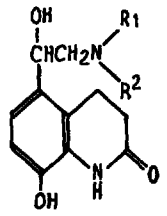
(71) We, OTSUKA PHARMACEUTICAL CO., LTD., a Japanese Company, of No. 9, Kanda Tsukasa-Cho, 2-Chome, Chiyoda-Ku, Tokyo, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the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

This invention relates to 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril deriva-

tives and to a process for preparing the same.

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).

According to one aspect of the present invention there are provided 5- [1 - hydroxy - 2 - (substituted - amino)] ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivatives of the following general formula (I):



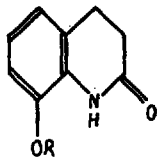
(I)

wherein R^1 and R^2, 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^1 and R^2 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 another aspect of the present invention there is provided a pharmaceutical composition including such a derivative.

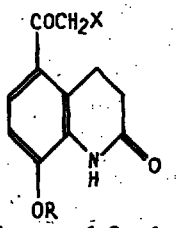
This invention also provides a process for preparing the 5 - [1 - hydroxy - 2 - (substituted - amino)] ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivatives represented by the formula (I) which comprises the steps of

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



(VII)

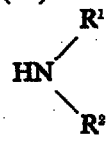
wherein R represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, with a haloacetyl halide in the presence of absence of a solvent and in the presence of a Lewis acid catalyst to prepare a 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the following general formula (IV):



(IV)

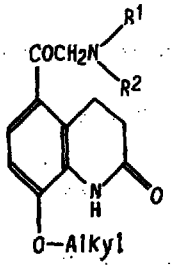
wherein R is as defined above and X represents a halogen atom,

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

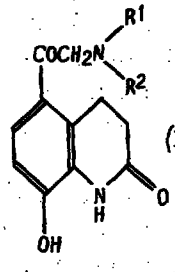


(III)

wherein R^1 and R^2 are as defined above, in the presence or absence of a solvent to prepare a 5 - substituted - aminoacetyl - 8 - alkoxy (or 8 - hydroxy) - 3,4 - dihydrocarbostyril derivative of the following general formula (IIa) and/or (IIb):



(IIa)



(IIb)

wherein the term "Alkyl" represents an alkyl group having 1 to 4 carbon atoms and R^1 and R^2 are as defined above, de-alkylating the resultant 8 - alkoxy derivatives of the general formula (IIa) with a hydrogen halide to produce the 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril of the general formula (IIb), and

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

The 5 - [1 - hydroxy - 2 - (substituted - amino) ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivatives of the formula (I) and salts thereof are novel compounds and exhibit a β - adreno - receptor stimulating activity and, therefore, are useful as bronchodilators, peripheral vasodilators or anti - hypertensive agents, particularly for treating bronchial asthma.

The term "alkyl" as used herein means a straight or branched chain alkyl group having from 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 from 1 to 4 carbon atoms and includes, 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 from 4 to 6 carbon atoms and includes, for example, a cyclopentyl, cyclobutyl or cyclohexyl group.

The term "5- or 6-membered substituted or unsubstituted heterocyclic ring" as used herein means a heterocyclic group containing 1 or 2 nitrogen, oxygen or sulphur atoms as hetero atoms, such as a pyrrolipyrrolidinyl, piperidino, piperidinyl, morpholino, morpholinyl, piperazino or piperazinyl group which may be unsubstituted or substituted with an alkyl group having from 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.

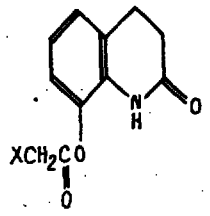
The compounds of the present invention represented by the formula (I) may be prepared from an 8 - substituted - 3,4 - dihydrocarbostyril according to the reaction scheme, shown in the single Figure of the accompanying drawings wherein R, R^1, R^2 and X are as hereinbefore defined.

The 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (VII) used as a starting material in the preparation of the compounds of the general formula (IV) is a known compound and can 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).

As illustrated in the reaction scheme, the 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril represented by the formula (IV) which is an intermediate in the process of this invention may be prepared in one step by reacting a corresponding 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (VII) with a haloacetyl halide in the absence or presence of a solvent and in the presence of a Lewis acid catalyst (route A).

The compound of the formula (IV) wherein R is hydrogen atom may also be prepared by the alternative routes (B)+(B') and (C)+(C') starting from 8 - hydroxy - 3,4 - dihydrocarbostyril (the formula (VII) wherein R represents a hydrogen atom).

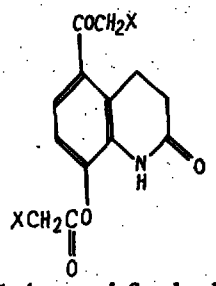
In the route (B)+(B'), the reaction between the 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and the haloacetyl halide results in the production of an 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the general formula (V):



(V)

wherein X is a halogen atom, which is then subjected to the rearrangement of the haloacetyl group to form the intermediate of general formula (IV).

In the route (C)+(C'), the reaction between the starting material (VII) and the haloacetyl halide results in the production of a 5 - haloacetyl - 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the general formula (VI):



(VI)

wherein X is as defined above, which is then subjected to hydrolysis of the 8 - haloacetyl group to form the intermediate of general formula (IV).

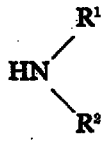
In practice, the reaction between the 8 - hydroxy - 3,4 - dihydrocarbostyril and the haloacetyl halide proceeds *via* a combination of the above-described three reaction routes, (A), (B)+(B') and (C)+(C'). Therefore, the reaction product is obtained as a mixture of the compounds of the formulae (IV), (V) and (VI). Generally, when the reaction is conducted at relatively low temperatures, the resulting product is a mixture of the compounds of the formulae (IV) and (V) with a small amount of the compound of the formula (VI), whereas if the reaction is conducted at relatively high temperatures, the resulting product is a mixture of the compounds of the formulae (IV) and (VI) with a small amount of the compound of the formula (V).

Isolation of the compounds of the formulae (IV), (V) or (VI) from the reaction product can be advantageously carried out by well-known procedures, for example, by fractional crystallization.

In a preferred isolation procedure, after completion of the reaction, the solvent used is removed by distillation to obtain a residue or the reaction mixture is poured into

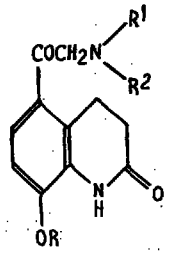
crushed ice to precipitate crystals. The residue or the crystals are washed with hot water or cool methanol and the insoluble substances are recrystallized from methanol to obtain a 5 - haloacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IV). The residual methanolic mother liquor is concentrated to dryness under reduced pressure, and the residue is recrystallized from acetone to obtain an 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the formula (V). The resulting acetone mother liquor is then concentrated to dryness under reduced pressure, and the residue is recrystallized from acetone or ethyl acetate to obtain a 5 - haloacetyl - 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the formula (VI).

The thus-obtained 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril intermediate (when R is an alkyl group, a 5 - haloacetyl - 8 - alkoxy - 3,4 - dihydrocarbostyril and when R is a hydrogen atom, a 5 - haloacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril) of the formula (IV) is then reacted with ammonia or a primary or secondary organic amine of the general formula (III):



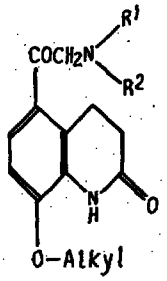
(III)

wherein R^1 and R^2 are as defined above, in the presence or absence of a solvent to obtain a 5 - substituted - aminoacetyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the general formula (II):



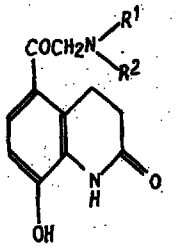
(II)

wherein R, R^1 and R^2 are as defined above, i.e., when R is an alkyl group, a 5 - substituted - aminoacetyl - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative represented by the formula (IIa):



(IIa)

wherein "Alkyl" represents an alkyl group having from 1 to 4 carbon atoms and R^1 and R^2 are as defined above or, when R is a hydrogen atom, a 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril represented by the formula (IIb):



(IIb)

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

The 8 - alkoxy compound of the formula (IIa) as obtained above may then be dealkylated with a hydrogen halide such as hydrogen bromide to form the corresponding 8 - hydroxy compound of the formula (IIb).

The 5 - [1 - hydroxy - 2 - (substituted - amino)] ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the formula (I) of the present invention may be prepared by reducing the above-obtained 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the formula (IIb).

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

The haloacetyl halides which are used in the present invention as reactants in the preparation of the compounds of the formula (IV) comprise those having a chlorine, bromine, iodine or fluorine atom as the halogen atom, with chloroacetyl chloride being preferred.

In the reaction route (A), a usual Lewis acid may be used as the catalyst, for example, aluminium chloride, aluminium bromide, zinc chloride, ferric chloride, stannic chloride, boron trifluoride or titanium chloride, with aluminium chloride being preferably used. The catalyst is generally used in an amount of from 2 to 10 moles, preferably from 3 to 6 moles, per mole of the 8 - substituted - 3,4 - dihydrocarbostyril of the general formula (VII).

This reaction can be effected in the absence of a solvent but the reaction proceeds more smoothly in an inert organic solvent, suitable examples of which are carbon disulphide, nitrobenzene, diethyl ether and dioxane, preferably, carbon disulphide. These inert organic solvents are usually used in a volume of 0.5 to 20, preferably 2 to 10 times the volume of the reactants. The reaction can be advantageously carried out under anhydrous condition.

Reaction (A) is generally conducted using

from an equimolar amount to a large excess of the haloacetyl halide, preferably 2 to 20 moles, most preferably from 2 to 10 moles, of the haloacetyl halide per mole of the 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VII). The reaction prooceds 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 hours, preferably from 1 to 10 hours.

Reaction (B) can be carried out using the same amount of the same catalyst as used in reaction (A) with the same solvent as used in reaction (A) or with no solvent. The reaction can be carried out using from an equimolar amount to a large excess of the haloacetyl halide, preferably from 2 to 20 moles, most preferably from 2 to 10 moles, per mole of the 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VII) at a temperature of from room temperature to 150°C, preferably from room temperature to 80°C, for from 1 to 20 hours, preferably from 1 to 10 hours.

Reaction (B') to obtain a 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril of the formula (IV) from the 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the formula (V) obtained in reaction (B) as above described is generally known as a Fries rearrangement, and may be carried out using the same catalyst as in reaction (A) in an amount of from 2 to 10 moles, preferably from 3 to 6 moles, per mole of the compound of the formula (V) with the same solvent as in reaction (A) or with no solvent. The reaction temperature may be from room temperature to 150°C, preferably from room temperature to 80°C and the reaction time is generally from 1 to 20 hours, preferably from 1 to 10 hours. This reaction can proceed in the presence of any haloacetyl halide which remains unreacted in the previous reaction system (B). It has been found that the presence of the haloacetyl halide improves the yield of the product, the 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril of the formula (IV).

Reaction (C) may be carried out using the same amount of the same catalyst as used in reaction (A) in the same solvent as used in reaction (A) or with no solvent. The haloacetyl halide is generally used in from an equimolar amount to a large excess relative to the 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VII), but preferably in an amount of from 2 to 20 moles, most preferably from 2 to 10 moles, per mole of the 8 - substituted - 3,4 - dihydrocarbostyril of the formula (VII). The reaction temperature is generally from room temperature to 150°C, preferably from room temperature to 80°C, and the reaction time is generally from 1 to 20 hours, preferably from 1 to 10 hours.

Reaction (C') to obtain the compound of the formula (IV) from the above obtained 5 - haloacetyl - 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the formula (VI) may be conducted using a catalyst, for example, a basic substance such as an alkali metal hydroxide or carbonates, e.g., sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate or an inorganic acid, e.g., hydrochloric acid, sulphuric acid or phosphoric acid in the presence of a solvent, for example, water or a lower alcohol such as ethanol, methanol or *iso* - propanol. The amount of the catalyst employed varies depending upon the type of the catalyst to be used. For example, hydrochloric acid or sodium hydroxide is used in an amount of from 1 to 5 moles per mole of the 5 - haloacetyl - 8 - haloacetoxy - 3,4 - dihydrocarbostyril of the formula (VI). The reaction generally proceeds at a temperature of 0° to 150°C for 0.5 to 5 hours, but it is advantageous to carry out the reaction at a temperature of from 0° to 40°C when a basic substance is used as a catalyst and at a temperature of 70° to 100°C when an inorganic acid is used as a catalyst.

The amines of the formula (III) which may be used as a reactant in the preparation of the 5 - substituted - aminoacetyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the formula (IIb) or (IIa) include alkylamines, for example, methylamine, ethylamine, *n* - propylamine, *iso* - propylamine, *n* - butylamine, *sec* - butylamine and *tert* - butylamine; cycloalkylamines, for example, cyclobutylamine, cyclopentylamine and cyclohexylamine; aralkylamines, for example, benzylamine, α - methylbenzylamine, α,α - dimethylbenzylamine, phenethylamine and α,α dimethylphenethylamine; and substituted or unsubstituted heterocyclic amines, for example, pyrrolidine, piperidine, morpholine, piperazine, 2 - methylpiperidine, 3 - methylpiperidine and N - methylpiperazine.

The reaction between the 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril intermediate of the formula (IV) and ammonia or the amine of the formula (III) may be carried out in the absence of a solvent since the amine of the formula (IV) *per se* also serves as a solvent but it is advantageous to conduct this reaction in 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 preferred.

This reaction may be effected using from

an equimolar amount to, especially in the absence of the solvent, a large excess of ammonia or the amine of the formula (III), preferably from 2 to 10 moles of the amine per mole of the 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril of the formula (IV), at from room temperature to a refluxing temperature of the reaction system, preferably from 40° to 100°C, at from atmospheric pressure to 10 atms.

Thus, when 8 - hydroxy - 3,4 - dihydrocarbostyril is used as a starting material, a 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril of the formula (IIb) is obtained, which can be subjected to the subsequent reduction reaction. When the 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (VII) wherein R is an alkyl group is used as a starting material, the corresponding 5 - substituted - aminoacetyl - 8 - alkoxy - 3,4 - dihydrocarbostyril of the formula (IIa) is obtained. The resulting 5 - substituted - amino - acetyl - 8 - alkoxy - 3,4 - dihydrocarbostyril (IIa) may then be reacted with a hydrogen halide to dealkylate the 8 - position of the carbostyril moiety thereby obtaining the compound (IIb).

The hydrogen halide used in this dealkylation may be, 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, *iso*-propanol or, preferably water, in the form of a 10 to 50%, preferably 47%, aqueous solution of hydrogen bromide.

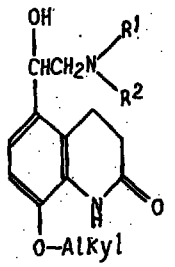
This dealkylation reaction is generally carried out using the hydrogen halide in from an equimolar amount to, preferably, a large excess with respect to the compound (IIa) by heating at a temperature of from 100° to 150°C, preferably at reflux, for from 1 to 20 hours, preferably from 3 to 10 hours.

The reduction of the above obtained 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the formula (IIb) to a 5 - [1 - hydroxy - 2 - (substituted - amino)] ethyl - 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 by catalytic reduction with hydrogen in the presence of a hydrogenation catalyst such as palladium black, palladium - on - carbon, Raney nickel, platinum black or platinum oxide.

The 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 (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 a reducing agent, the solvent is preferably water or alcohols 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 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 as a pressure of from atmospheric pressure to 100 atms., preferably from 1 to 50 atms., 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 desirable to carry out the above catalytic reduction at a temperature higher than about 50°C at atmospheric pressure or at a temperature higher than room temperature under pressure.

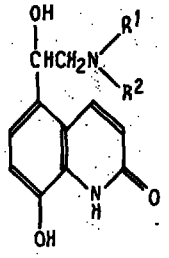
Alternatively, the compound of the formula (I) of the present invention may be prepared by reducing the previously prepared 5 - substituted - aminoacetyl - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative of the formula (IIa), in the same manner as described above with respect to the reduction of the compound of the formula (IIb), to a 5 - [1 - hydroxy - 2 - (substituted - amino)] ethyl - 8 - alkoxy - 3,4 - dihydrocarbostyril derivative of the following general formula (VIII):



(VIII)

wherein R^1, R^2 and "Alkyl" are as defined above, which is then dealkylated with a hydrogen halide such as hydrogen bromide in the same manner as described above with respect to the dealkylation from the compound (IIa) to the compound (IIb). Compounds of the general formula (VIII) fall within the definition of certain compounds described and claimed in our copending Patent Application No. 55929/74 (Serial No. 1,496,770) of even date.

Further, a compound of the formula (I) may also be prepared by reducing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyril derivative of the following general formula (IX):

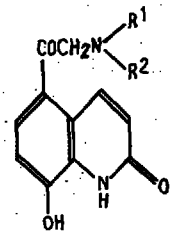


(IX)

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

The 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - carbostyril derivatives of the formula (IX) which can be used as a reactant in the above described reduction can be obtained according to the process disclosed in the Applicants' copending Patent Application No. 55900/74 (Serial No. 1,496,769) of even date.

The compounds of the formula (I) may also be prepared by reducing a compound of the following general formula (X):



(X)

wherein R^1 and R^2 are as defined in Claim 1 or an acid addition salt thereof. This method of preparation is described in Examples 26 and 34 hereinafter. Compounds of the general formula (X) are described and claimed in our copending Patent Application No. 29524/77 (Serial No. 1,496,872) of even date.

The compounds of formulae IIa and IIb form the subject of our copending Patent Application No. 28862/77 (Serial No. 1,496,873) of even date.

These reductions can be conducted under the same conditions as described above with respect to the reduction of the compound of the formula (IIb) in the presence of the same catalyst as used therein.

Both the compounds of the formula (II) 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 of the formula (I) and acid addition salts thereof exhibit a stimulating activity on β - adreno - receptor and, therefore, are very useful as pharmaceutical 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 formula (I) are the following basic compounds and their hydrochlorides, sulphates, phosphates, maleates, fumarates and oxalates.

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

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

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

5 - [1 - Hydroxy - 2 - (α - methylbenzylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril

5 - [(1 - Hydroxy - 2 - (α,α - dimethylphenethylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

EXAMPLE 1

24.3 Grams of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and 68 g of chloroacetyl chloride were added to 130 ml of carbon disulphide, and 200 g of aluminium chloride were added slowly to the mixture while stirring and cooling in ice-water. The mixture was stirred for 6 hours at a temperature of 60 to 70°C and carbon disulphide was removed by distillation. The resulting residue was poured into 500 ml of ice-water. The precipitated crystals were filtered, washed with water and recrystallized twice from methanol to give 8.0 g of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) as light yellow crystals having a melting point of 189 to 191°C.

EXAMPLE 2

13 Grams of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and 20 g of chloroacetyl chloride were dissolved in 100 ml of nitrobenzene, 40 g of aluminium chloride were added slowly to the mixture and the mixture was then stirred for 15 hours at a temperature of 70 to 75°C. The mixture was then steam-distilled to remove nitrobenzene. After allowing the mixture to cool, the precipitated crystals were filtered, washed with hot water and recrystallized from methanol to give 7.2 g of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) as light yellow crystals having a melting point of 189 to 190°C.

EXAMPLE 3

66 Grams of chloroacetyl chloride and 30 ml of nitrobenzene were added to 17 g of 8 - methoxy - 3,4 - dihydrocarbostyril (VII); 100 g of aluminium chloride were added slowly to the resulting mixture while cooling with ice and the mixture was then stirred for 30 minutes at room temperature. After allowing the mixture to stand for an additional 30 minutes, the mixture was poured into 700 ml of ice-water. The precipitate thus formed was filtered, washed with ethanol and recrystallized from methanol to give 20 g of white needle-like crystals having a melting point of 187 to 188°C. The crystals thus obtained were confirmed by NMR and IR spectra and elemental analysis to be 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV).

EXAMPLE 4

33 Grams of chloroacetyl chloride and 80 ml of carbon disulphide were added to 8.5 g of 8 - methoxy - 3,4 - dihydrocarbostyril (VII); 50 g of aluminium chloride were added slowly to the resulting mixture while cooling with ice and the mixture was then stirred for 2 hours at room temperature. The carbon disulphide layer was removed by decantation, and crushed ice was added to the remaining solution to crystallize the product. The precipitated crystals thus obtained were filtered, washed with ethanol and recrystallized from methanol to give 11 g of white needle-like crystals having a melting point of 187 to 188°C. The product thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV).

EXAMPLE 5

24.3 Grams of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and 68 g of chloroacetyl chloride were added to 130 ml of carbon disulphide, and 200 g of aluminium chloride were added slowly to the mixture while stirring and cooling with ice-water. The resulting mixture was then allowed to react for 4 hours under ice-cooling to give 8 - chloroacetoxy - 3,4 - dihydrocarbostyril (V). The reaction mixture was stirred for 2 hours at a temperature of 60 to 70°C and carbon disulphide was distilled off. The resulting residue was poured into 500 ml of ice-water and the precipitated crystals were filtered, washed with water and recrystallized twice from methanol to give 8.0 g of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) as light yellow crystals having a melting point of 189 to 191°C.

The 8 - chloroacetoxy - 3,4 - dihydrocarbostyril (V) produced as an intermediate in the above procedure was isolated from an aliquot of the reaction mixture and found to have a melting point of 183 to 186°C after recrystallization from acetone.

EXAMPLE 6

40 Grams of aluminium chloride were added to 11.5 g of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII), and the mixture was thoroughly stirred. 21 Grams of chloroacetyl chloride were then added slowly to the mixture while cooling with ice-water; the resulting mixture was stirred at a temperature of 35 to 40°C for 2 hours and then distilled to remove any excess chloroacetyl chloride. The residue thus obtained was poured into crushed ice, and the precipitated crystals were filtered, washed with water and recrystallized from acetone to give 5.6 g of 8 - chloroacetoxy - 3,4 - dihydrocarbostyril (V) as light yellow crystals having a melting point of 182 to 184°C.

EXAMPLE 7

13 Grams of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and 20 g of chloroacetyl chloride were dissolved in 100 ml of nitrobenzene, and 40 g of aluminium chloride were added slowly to the mixture which was then stirred at a temperature of 70 to 75°C for 15 hours. The nitrobenzene was then removed by steam-distillation. After allowing the mixture to cool, the precipitated crystals were filtered, washed with hot water and recrystallized from methanol to give 7.2 g of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) as light yellow crystals having a melting point of 189 to 190°C.

EXAMPLE 8

30 Grams of aluminium chloride were added slowly while ice-cooling and stirring to 6.0 g of 8 - hydroxy - 3,4 - dihydrocarbostyril (VII) and 15.0 g of chloroacetyl chloride and the mixture was then stirred at a temperature of 55 to 60°C for 6 hours to produce 5 - chloroacetyl - 8 - chloroacetoxy - 3,4 - dihydrocarbostyril (VI). 50 Millilitres of a 10% aqueous hydrochloric acid were added to the reaction mixture which was then stirred for 3 hours at a temperature of 95 to 100°C. After allowing the mixture to cool, the precipitated crystals were filtered, washed with water and recrystallized from methanol to give 2.7 g of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) as light yellow crystals having a melting point of 189 to 190°C.

In the above procedure, an aliquot of the reaction mixture was taken out from the reaction system before the hydrolysis with hydrochloric acid and poured into ice-water. The precipitated crystals were filtered, washed with hot water and recrystallized from dimethylformamide - methanol (1:1 by volume) to give 5 - chloroacetyl - 8 - chloroacetoxy - 3,4 - dihydrocarbostyril (VI) as

light yellow crystals having a melting point of 206 to 207°C.

EXAMPLE 9

4 Grams of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 8 were dissolved in 50 ml of *iso*-propanol, and 20 g of *iso*-propylamine (III) were added to the solution which was then stirred at a temperature of 60°C for 3 hours. The reaction mixture was concentrated to a volume of 1/3 to 1/4 the original volume and saturated with dried hydrogen chloride gas. After allowing the mixture to cool, the precipitate thus formed was filtered and recrystallized from ethanol to give 3.5 g of a colourless amorphous material having a melting point of 274 to 275°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *iso* - propylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 10

3 Grams of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 8 were dissolved in 40 ml of *iso*-propanol, and 3 g of methylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 30 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional hour. The reaction mixture was then concentrated to a volume of 1/3 the original volume and adjusted to a pH of 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.5 g of a colourless amorphous material having a melting point of 254 to 256°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - methylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 11

3.54 Grams of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril prepared as described in Example 8 were dissolved in 30 ml of *iso*-propanol, and 2.7 g of ethylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 20 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional 40 minutes. The reaction mixture was then concentrated to a volume of 1/3 the original volume and adjusted to a pH of 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.9 g of a colourless amorphous material having a melting point of 258 to 260°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - ethylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 12

4 Grams of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 8 were dissolved in 60 ml of *iso*-propanol, and 20 g of *tert* - butylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 20 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional 40 minutes. The reaction mixture was then concentrated to a volume of 1/2 the original volume and adjusted to a pH of 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized repeatedly from the mixture of ethanol and acetone (1:2 by volume) to give 2.0 g of a colourless amorphous material having a melting point of 253 to 255°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis as 5 - *tert* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 13

3 Grams of 5 - chloroacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Example 8 were dissolved in 40 ml of iso-propanol, and 10 g of *sec*-butylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 20 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional 2.5 hours. The reaction mixture was then concentrated to a volume of 1/3 the original volume and saturated with dry hydrogen chloride gas. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.8 g of a colourless amorphous material having a melting point of 269 to 271°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *sec* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 14

4 Grams of 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Examples 3 and 4 were dissolved in 50 ml of *iso* - propanol, and 20 g of *iso* - propylamine (III) were added to the solution which was then stirred for 3 hours at a temperature of 60°C. The reaction mixture was then concentrated to a volume of 1/3 to 1/4 the original volume and saturated with dry hydrogen chloride gas. After allowing the mixture to cool, the precipitate thus formed was filtered and re-

crystallized from ethanol to give 3.5 g of a colourless needle-like crystalline material having a melting point of 208 to 209°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *iso* - propylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril hydrochloride.

EXAMPLE 15

3 Grams of 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Examples 3 and 4 were dissolved in 40 ml of *iso* - propanol, and 3 g of methylamine (III) were added dropwise to the solution over a period of 30 minutes while stirring at a temperature of 60°C. After completion of the addition, the mixture was stirred while heating at that temperature for an additional hour. The reaction mixture was then concentrated to a volume of 1/3 the original volume and adjusted to a pH of 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.5 g of a colourless needle-like crystalline material having a melting point of 232 to 234°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - methylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride.

EXAMPLE 16

2.54 Grams of 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Examples 3 and 4 were dissolved in 30 ml of *iso*-propanol, and 2.7 g of ethylamine (III) were added dropwise to the solution over a period of 20 minutes while stirring at a temperature of 60°C over 20 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional 40 minutes. The reaction mixture was then concentrated to a volume of 1/3 the original volume and adjusted to a pH of 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.9 g of a colourless needle-like material having a melting point of 224 to 227°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - ethylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride.

EXAMPLE 17

4 Grams of 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Examples 3 and 4 were dissolved in 60 ml of *iso* - propanol, and 20 g of *tert* - butylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 20 minutes. After completion of the addition, the mixture was stirred while heating at that temperature for an additional 40 minutes. The reaction mixture was then concentrated to a volume of 1/2 the original volume and adjusted to a pH of from 1 to 2 with concentrated hydrochloric acid. The precipitate thus formed was filtered and recrystallized from a mixture of ethanol and acetone (1:2 by volume) to give 2.0 g of a colourless amorphous material having a melting point of 208 to 210°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *tert* - butylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride.

EXAMPLE 18

3 Grams of 5 - chloroacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IV) prepared as described in Examples 3 and 4 were dissolved in 40 ml of *iso* - propanol, and 10 g of *sec* - butylamine (III) were added dropwise to the solution while stirring at a temperature of 60°C over 20 minutes. The reaction mixture was then concentrated to a volume of 1/3 the original volume and saturated with dry hydrogen chloride gas. The precipitate thus formed was filtered and recrystallized from ethanol to give 1.8 g of colourless needle-like crystals having a melting point of 212 to 214°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *sec* - butylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbo - styril (IIa) hydrochloride.

EXAMPLE 19

1 Gram of 5 - *iso* - propylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride prepared as described in Example 14 was dissolved in 10 ml of a 47% aqueous hydrogen bromide solution, and the mixture was refluxed at a bath temperature of 120 to 130°C for 2.5 hours. 20 Millilitres of water were then added to the mixture which was then adjusted to a pH of 6.5 to 7.5 with sodium bicarbonate. The precipitate thus formed was filtered, washed with water and dried. The material thus obtained was dissolved in *iso* - propanol and the solution was saturated with dry hydrogen chloride gas. The precipitate was filtered and recrystallized from ethanol to give 0.5 g of a colourless amorphous material having a melting point of 274 to 275°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *iso* - propylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 20

0.7 Gram of 5 - methylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa)

hydrochloride prepared as described in Example 15 was dissolved in 10 ml of a 47% aqueous hydrogen bromide solution, and the mixture was refluxed at a bath temperature of 120 to 130°C for 4 hours. The reaction mixture was then worked up in the same manner as described in Example 19 to give 0.5 g of a colourless amorphous material having a melting point of 254 to 256°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - methylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 21

0.9 Gram of 5 - *tert* - butylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride was dissolved in 10 ml of a 47% aqueous hydrogen bromide solution, and the resulting solution was then worked up in the same manner as described in Example 19 to obtain 0.2 g of a light yellow amorphous material having a melting point of 253 to 255°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *tert* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 22

0.5 Gram of 5 - *sec* - butylaminoacetyl - 8 - methoxy - 3,4 - dihydrocarbostyril (IIa) hydrochloride prepared as described in Example 18 was dissolved in 10 ml of a 47% aqueous hydrogen bromide solution, and the resulting solution was then worked up in the same manner as described in Example 19 to give 0.24 g of a colourless amorphous material having a melting point of 269 to 271°C. The material thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - *sec* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride.

EXAMPLE 23

2.0 Grams of 5 - *iso* - propylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride prepared as described in Example 19 were dissolved in 40 ml of water, and 0.5 g of palladium black as a catalyst was added to the solution. The mixture was stirred at a temperature of 70 to 75°C under atmospheric pressure in the presence of hydrogen gas so as to absorb hydrogen. After completion of the reduction, the catalyst was filtered off and the filtrate was concentrated to dryness under reduced pressure. The water remaining in the resulting residue was then completely removed using ethanol, and acetone was added to the residue to crystallize the product. Recrystallization from a mixture of ethanol and acetone (1:2 by volume) gave 1.1 g of a colourless amorphous material having a melting point of 199 to 201°C. The product thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride.

EXAMPLE 24

1.5 Grams of 5 - *tert* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride prepared as described in Example 21 were dissolved in 35 ml of water, and 1.0 g of palladium - on - carbon as a catalyst was added to the solution. The mixture was shaken at a temperature of 50 to 60°C under a pressure of 4 to 5 atms. in the presence of hydrogen gas to absorb the hydrogen. After completion of the reduction, the catalyst was filtered off and the filtrate was concentrated to dryness under reduced pressure. Acetone was added to the residue to crystallize the product. Recrystallization from a mixture of methanol and acetone (1:2 by volume) gave 0.8 g of a colourless amorphous material having a melting point of 240 to 241°C. The product thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - (1 - hydroxy - 2 - *tert* - butylamino) ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride.

EXAMPLE 25

2.0 Grams of 5 - *sec* - butylaminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) prepared as described in Example 13 were dissolved in 100 ml of methanol, and 0.8 g of sodium borohydride was added slowly to the solution while stirring under ice-cooling. The mixture was then stirred at that temperature for 15 minutes and then at room temperature for one hour. The mixture was adjusted to a pH of 1.5 to 2 with concentrated hydrochloric acid and the solvent was then distilled off under reduced pressure. 30 Millilitres of ethanol were then added to the residue and the mixture was again concentrated to dryness under reduced pressure to remove water. 50 Millilitres of absolute ethanol were added to the resulting residue, and the mixture was adjusted to a pH of 7 to 8.5. The precipitate thus formed was filtered off, and the filtrate was concentrated to dryness under reduced pressure and the residue was recrystallized from a mixture of methanol and acetone (1:2 by volume) to give 1.3 g of a colourless amorphous material having a melting point of 183 to 184°C. The product thus obtained was confirmed by NMR and IR spectra and elemental analysis to be 5 - (1 - hydroxy - 2 - *sec* - butylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride.

EXAMPLE 26

0.7 Gram of palladium black and 130 ml

of water were added to 1.5 g of 5 - (α - methylbenzylaminoacetyl) - 8 - hydroxycarbostyril (X) hydrochloride, and the mixture was reacted under a hydrogen pressure of 4 atms, at a temperature of 60°C while shaking the mixture. After completion of the reaction, the catalyst was filtered off and the aqueous filtrate was concentrated to dryness. Acetone was added to the residue to crystallize the product which was then washed with 100 ml of ethanol and recrystallized from a mixture of methanol and ethyl actate to obtain 0.8 g of white amorphous 5 - (1 - hydroxy - 2 - benzylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride. The identity of the product obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 27

0.1 Gram of palladium black and 50 ml of water were added to 0.4 g of 5 - (1 - hydroxy - 2 - benzylamino)ethyl - 8 - hydroxycarbostyril (IX) hydrochloride dihydrate, and the mixture was reacted at room temperature and at atmospheric pressure in a hydrogen atmosphere for 8 hours, while shaking the mixture. After completion of the reaction, the catalyst was filtered off, and the aqueous filtrate was concentrated to dryness. The residue thus obtained was recrystallized from a mixture of methanol and acetone to obtain 0.2 g of white amorphous 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxycarbostyril (I) hydrochloride. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 28

0.7 Gram of palladium black and 100 ml of water were added to 1.4 g of 5 - (α - benzylaminoacetyl) - 8 - hydroxy - 3,4 - dihydrocarbostyril (IIb) hydrochloride, and the mixture was reduced at a temperature of 60°C at a hydrogen pressure of 4 atms. After completion of the reduction, the catalyst was filtered off and the resulting aqueous filtrate was concentrated to dryness. Acetone was then added to the residue to crystallize the product. The crystals thus obtained were washed with 100 ml of ethanol and recrystallized from a mixture of methanol and ethyl acetate to obtain 0.7 g of white amorphous 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I)) hydrochloride. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis:

EXAMPLE 29

0.05 Gram of platinum black and 100 ml of water were added to 1 g of 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydrocarbostyril (IX) hydrochloride, and the mixture was reduced at a hydrogen pressure of 2 atms. at 50°C for 10 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered off, and the aqueous filtrate was concentrated to dryness. The precipitate thus obtained was recrystallized from a mixture of methanol and acetone to obtain 0.9 g of white amorphous 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride having a melting point of 270 to 272°C. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 30

0.5 Gram of palladium black and 50 ml of water were added to 2 g of 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - carbostyril (IX), and the mixture was reduced at atmospheric pressure in a hydrogen atmosphere at a temperature of 70°C for 8 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered off and the aqueous filtrate was concentrated to dryness. The precipitate thus obtained was recrystallized from a mixture of methanol and acetone to obtain 1.7 g of white amorphous 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 31

0.1 Gram of palladium black and 30 ml of water were added to 1 g of 5 - (1 - hydroxy - 2 - *sec* - butylamino)ethyl - 8 - hydroxycarbostyril (IX) and the mixture was reduced at a hydrogen pressure of 3 atms. at a temperature of 60°C for 10 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered off, and the aqueous filtrate was concentrated to dryness. The precipitate thus obtained was recrystallized from a mixture of methanol and acetone to obtain 0.6 g of 5 - (1 - hydroxy - 2 - *sec* - butylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 32

0.5 Gram of 10% palladium-on-carbon and 50 ml of water were added to 1.5 g of 5 - (1 - hydroxy - 2 - *tert* - butylamino)-ethyl - 8 - hydroxycarbostyril (IX) hydrochloride, and the mixture was reduced at a hydrogen pressure of 5 atms. at a temperature of 75°C for 16 hours while shaking the mixture. After completion of the reduction, the catalyst was filtered and the aqueous

filtrate was concentrated to dryness. The precipitate thus obtained was recrystallized from a mixture of methanol and acetone to obtain 1.1 g of white amorphous 5 - (1 - hydroxy - 2 - *tert* - butylamino) - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) having a melting point of 240 to 241°C.. The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 33

100 Milligrams of palladium black and 50 ml of water were added to 300 mg of 5 - [1 - hydroxy - 2 - (1,1, - dimethylphenethylamino)]ethyl - 8 - hydroxycarbostyril (IX) hydrochloride monohydrate, and the mixture was reduced at a hydrogen pressure of 2.5 atms. at a temperature of 45 to 50°C for 8 hours. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was recrystallized from water to obtain 260 mg of an amorphous material having a melting point of 120 to 121°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 - (1,1 - dimethylphenethylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride dihydrate.

EXAMPLE 34

0.2 Gram of platinum oxide and 50 ml of water were added to 1.0 g of 5 - (1,1 - dimethylphenethylaminoacetyl) - 8 - hydroxycarbostyril (IX) hydrochloride 1/2 hydrate, and the mixture was reduced at a hydrogen pressure of 5 atms. at a temperature of 80°C for 20 hours. The catalyst was filtered off, and the filtrate was concentrated to dryness. The resulting residue was recrystallized from water to obtain 0.8 g of a white amorphous material having a melting point of 120 to 121°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 - (1,1 - dimethylphenethylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride dihydrate.

EXAMPLE 35

70 Millilitres of 47% aqueous hydrobromic acid was added to 1 g of 5 - (1 - hydroxy - 2 - *iso* - propylamino)ethyl - 8 - methoxy - 3,4 - dihydrocarbostyril (VIII) hydrochloride monohydrate, the mixture was heated under refluxing for 15 hours and concentrated to dryness. Acetone was added to the resulting residue to crystallize the product and the mixture was then adjusted to a pH of 8 with dilute aqueous sodium hydroxide solution. The precipitated crystals were filtered, washed with water and dissolved in ethanol. The solution was adjusted to a pH of 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 203 to 204°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 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride.

In the same manner as described in Example 35, the following compound of the formula (I) was obtained from the corresponding 8 - methoxy compound of the formula (VIII):

5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril hydrochloride having a melting point of 270 to 272.5°C (with decomposition).

EXAMPLE 36

1.5 Grams of 5 - piperidinoacetyl - 8 - hydroxycarbostyril (IIb) hydrochloride were dissolved in 100 ml of water, and 0.5 g of palladium-on-chacoal and 0.2 g of palladium black were added to the solution. The resultant mixture was catalytically reduced under atmospheric pressure in a hydrogen atmosphere for 4 days at a temperature of 70°C while shaking the mixture. 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 was then allowed to cool. The precipitate which formed upon cooling was recrystallized from *iso* - propanol to obtain 0.8 g of white amorphous 5 - (1 - hydroxy - 2 - piperidino)-ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril (I) hydrochloride 1/2 hydrate having a melting point of 136 to 139°C (with decomposition). The identity of the product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

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 determined 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 as shown in Table I 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 conditions 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
5-(1-Hydroxy-2-*iso*-propylamino)-ethyl-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride	0	21.4	50.0	85.0	100		—	—	—
5-(1-Hydroxy-2-*tert*-butylamino)-ethyl-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride	4.3	38.7	85.5	100	100		—	—	—
5-[1-Hydroxy-2-(α,α-dimethylphenethylamino)]-ethyl-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride	0	4.7	14.2	45.2	76.4	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

Further, the acute toxicity of the test compounds shown in Table II below was determined using 5 to 6 groups each containing 10 male rats (dd strain; body weight, 18 to 22 g) which had been fasted for 12 hours prior to the test. (Salbutamol and iso - proterenol were used as controls).

The LD_{50} (50% lethal dose) results are as follows:

TABLE II

Compound	LD_{50} (mg/Kg) i.v.	p.o.
5-(1-Hydroxy-2-*iso*-propylamino)ethyl-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride	110 (92–131)	1770 (1283–2443)
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 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 such as are well known in the art.

Pharmaceutical compositions according to the present invention generally comprise at least one compound of the present invention together with pharmaceutical carriers or diluents such as are commonly employed in conventional pharmaceutical compositions. The compositions of this invention may contain other active component 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 sublingal 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 solution, suspension or dry preparation which is reconstituted instantaneously with a vehicle for injection just before administration.

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

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

Formulation 1

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

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

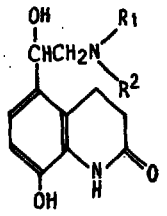
Formulation 2

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

Component	Amount
5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril	50 mcg
Oleic Acid	10 mcg
Dichlorodifluoromethane	57 mcg
Trichlorofluoromethane	25 mcg

WHAT WE CLAIM IS:—

1. A 5 - [1 - hydroxy - 2 - (substituted - amino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the following general formula (I):



(I)

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

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

4. A derivative according to Claim 1, wherein R^1 represents a hydrogen atom, R^2 represents a benzyl or α-methylbenzyl group.

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

6. A derivative according to Claim 1, wherein R^1 and R^2 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 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 - methylpiperizino group.

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

9. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

10. 5 - (1 - Hydroxy - 2 - *sec* - butylamine)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

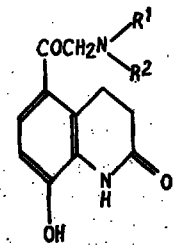
11. 5 - [1 - Hydroxy - 2 - (α - methylbenzylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

12. 5 - [1 - Hydroxy - 2 - (α,α - dimethylphenethylamino)]ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril.

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

14. An acid addition salt according to Claim 13, which is a hydrochloride, a sulphate, a phosphate, a maleate, a fumarate or an oxalate.

15. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative as defined in any of Claims 1 to 7, or an acid addition salt thereof, which comprises reducing a 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the following general formula (IIb):



(IIb)

wherein R^1 and R^2 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.

16. A process according to Claim 15, 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.

17. A process according to Claim 16, wherein the catalyst is used in an amount of from 0.1 to 0.5 mole per mole of said 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative.

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

19. A process according to any of Claims 16 to 18, wherein the pressure is from atmospheric to 50 atmospheres.

20. A process according to any of Claims 16 to 19, wherein the reduction is effected in the presence of water or methanol ethanol or *iso*-propanol as a solvent.

21. A process according to Claim 15, 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 aminoacetyl - 8 - hydroxy - 3,4 -

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dihydrocarbostyril derivative at a temperature of from 0° to 100°C under atmospheric pressure.

22. A process according to Claim 21, 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.

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

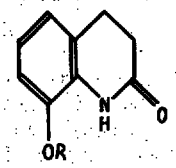
24. A process according to any of Claims 21 to 23, wherein lithium aluminium hydride is employed as the reducing agent and the reduction is effected in the presence of anhydrous ethyl ether, ethyl acetate or tetrahydrofuran as a solvent.

25. A process according to any of Claims 21 to 24, 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.

26. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 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 23, 25, 28 or 36.

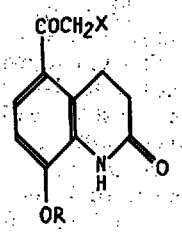
27. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyril derivative of the general formula (I) defined in Claim 1 or an acid addition salt thereof which comprises;

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



(VII)

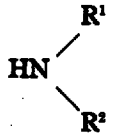
wherein R represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms with a haloacetyl halide in the presence or absence of a solvent and in the presence of a Lewis acid catalyst to prepare a 5 - haloacetyl - 8 - substituted - 3,4 - dihydrocarbostyril derivative of the following general formula (IV):



(IV)

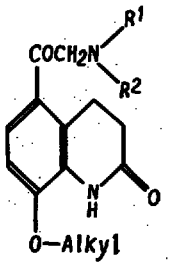
wherein R is as defined above and X represents a halogen atom;

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

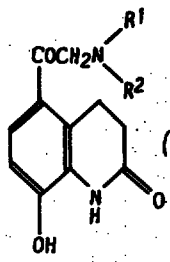


(III)

wherein R^1 and R^2 are as defined above, in the presence or absence of a solvent to prepare a 5 - substituted - aminoacetyl - 8 - hydroxy (or 8 - alkoxy) - 3,4 - dihydrocarbostyril derivative or the following general formula (IIa) or (IIb):



(IIa)



(IIb)

wherein "Alkyl" represents an alkyl group having 1 to 4 carbon atoms and R^1 and R^2 are as defined above, or an acid addition salt thereof, dealkylating the resulting 8 - alkoxy derivative or acid addition salt represented by the formula (IIa) with a hydrogen halide to produce the 5 - substituted - aminoacetyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative or acid addition salt of the general formula (IIb), and

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

28. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 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 the reaction scheme shown in the accompanying drawings.

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

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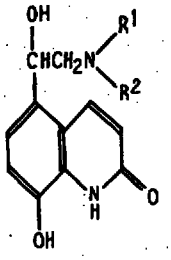


(IX)

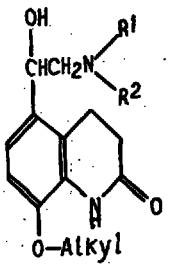
wherein R^1 and R^2 are as defined in Claim 1, or an acid addition salt thereof.

30. A process according to Claim 29, wherein the reduction is effected by using palladium black, palladium-on-carbon, platium 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-carbostyril 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.

31. A process according to Claim 29, wherein the reduction is effected by using lithium aluminium hydride or sodium boro-hydride as a reducing agent in an amount of from 2 to 10 moles per mole of said 5 - substituted aminoacetyl - 8 - hydroxy - carbostyril derivative at a temperature of from 0° to 100°C under atmospheric pressure.

32. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril or an acid addition salt thereof, substantially as hereinbefore described with reference to any one of the foregoing Examples 27, or 29 to 33.

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



(VIII)

wherein R^1 and R^2 are as defined in Claim 1 and the term "alkyl" means an alkyl group having from 1 to 4 carbon atoms, or an acid addition salt thereof.

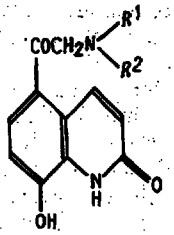
34. A process according to Claim 33, wherein the hydrogen halide is hydrogen bromide.

35. A process according to Claim 33 or 34, wherein the hydrogen halide is employed as a 10 to 50% by weight aqueous solution.

36. A process according to any of Claims 33 to 35, wherein the dealkylation is carried out using the hydrogen halide in from an equimolar amount to a large excess with respect to the compound of general formula (VIII) at a temperature of from 100° to 150°C for from 1 to 20 hours.

37. A process for the preparation of a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 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 the foregoing Example 35.

38. A process for the preparation of a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative of the general formula (I) defined in Claim 1, or an acid addition salt thereof, which comprises reducing a 5 - substituted - aminoacetyl - 8 - hydrocarbostyril derivative of the following general formula (X):



(X)

wherein R^1 and R^2 are as defined in Claim 1, substantially as hereinbefore described with reference to the foregoing Examples 26 or 34.

39. A process as claimed in Claim 14, in Claim 33 or in Claim 38, each substantially as hereinbefore described with reference to the reaction scheme shown in the accompanying drawing.

40. A 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative according to Claim 1 or an acid addition salt thereof, when prepared by a process as claimed in any of Claims 11 to 39.

41. A pharmaceutical composition which comprises a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyril derivative as claimed in any of Claims 1 to 14 or 40 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

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

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43. A pharmaceutical composition according to Claim 42 and in tablet form.

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

45. A pharmaceutical composition according to Claim 42 and substantially as hereinbefore described.

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

47. A method of alleviating bronchial asthma in a non-human mammal, which comprises administering to said mammal a pharmaceutically - effective amount of a pharmaceutical composition as claimed in any of Claims 41 to 45.

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

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

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