

PATENT SPECIFICATION

(11) 1 496 769

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- (21) Application No. 55900/74/
- (22) Filed 27 Dec. 1974/
- (31) Convention Application No. 49/012954
- (32) Filed 31 Jan. 1974 /
- (31) Convention Application No. 49/012953-
- (32) Filed 31 Jan. 1974
- (31) Convention Application No. 49/015115
- (32) Filed 5 Feb. 1974 /
- (31) Convention Application No. 49/015116
- (32) Filed 5 Feb. 1974 /
- (31) Convention Application No. 49/015953
- (32) Filed 7 Feb. 1974 /
- (31) Convention Application No. 49/019787
- (32) Filed 18 Feb. 1974 /
- (31) Convention Application No. 49/023604
- (32) Filed 27 Feb. 1974 /
- (31) Convention Application No. 49/130717
- (32) Filed 11 Nov. 1974 /
- (31) Convention Application No. 49/130725
- (32) Filed 11 Nov. 1974 /
- (31) Convention Application No. 49/130719
- (32) Filed 11 Nov. 1974
- (31) Convention Application No. 49/130727
- (32) Filed 11 Nov. 1974 /
- (31) Convention Application No. 49/130718
- (32) Filed 11 Nov. 1974 /
- (31) Convention Application No. 49/140340
- (32) Filed 4 Dec. 1974 /
- (31) Convention Application No. 49/140339
- (32) Filed 4 Dec. 1974 in
- (33) Japan (JP)
- (44) Complete Specification published 5 Jan. 1978
- (51) INT CL² C07D 215/22 A61K 31/47 C07D 401/06 413/06 (C07D 401/06 295/08) (C07D 413/06 215/22)
- (52) Index at acceptance
 - C2C 1532 1534 1562 213 215 220 226 22Y 246 247 250 251 255
 - 25Y 28X 29X 29Y 30Y 321 322 32Y 351 352 360 362 365
 - 36Y 388 509 50Y 620 625 633 650 652 672 761 762 790
 - 79Y LK TT

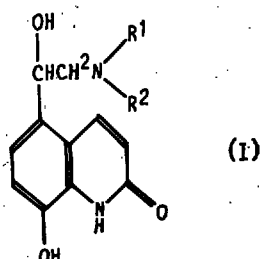
(54) 5-SUBSTITUTED ETHYL-8-HYDROXYCARBOSTYRIL DERIVATIVES AND PRODUCTION THEREOF

(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:—

It is well known that certain carbostyryl derivatives exhibit useful pharmaceutical

activities. Representative compounds of this type have been disclosed in *Journal of Medical Chemistry*, 15, No. 3, pp 260—266 (1972), in Japanese Patent Publication No. 38789/1971 and in *Chemical Abstracts*, 62, 16212e (1965).

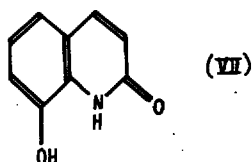
The present invention provides 5 - [1 - hydroxy - 2 - (substituted - amino)]ethyl - 8 - hydroxycarbostyryl derivatives having the following general formula (I):



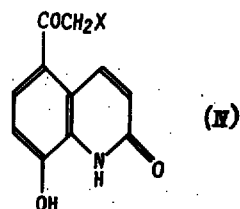
wherein R^1 and R^2 , which may be the same or different, each represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, an aralkyl group containing a straight or branched chain alkyl moiety having 1 to 4 carbon atoms or a cycloalkyl group having 4 to 6 carbon atoms, or R^1 and R^2 may, 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.

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

(1) reacting together an 8 - hydroxycarbostyryl represented by the following general formula (VII):

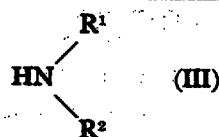


and a haloacetyl halide in the presence or absence of a solvent and in the presence of a Lewis acid catalyst to prepare a 5 - haloacetyl - 8 - hydroxycarbostyryl derivative represented by the following general formula (IV):

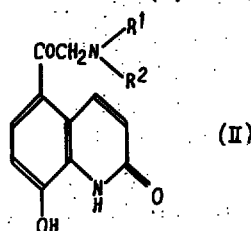


wherein X represents a halogen atom,

(2) reacting together the resulting 5 - haloacetyl - 8 - hydroxycarbostyryl derivative represented by the formula (IV) and ammonia or an amine represented by the following general formula (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 - hydroxycarbostyryl derivative represented by the following general formula (II):



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

(3) reducing the resulting 5 - substituted - aminoacetyl - 8 - hydroxycarbostyryl derivative represented by the formula (II) with hydrogen in the presence of a catalyst or with a reducing agent.

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

The term "alkyl" as used herein means a straight or branched chain alkyl group having 1 to 4 carbon atoms, and includes, for example, a methyl, ethyl, propyl, *iso* - propyl, butyl, *sec* - butyl and a *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, such as a phenylalkyl group, 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, such as for example, a cyclopentyl, cyclobutyl 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 a pyrrolidino, piperidino, morpholino, or piperazino group which may be unsubstituted or substituted with an alkyl group having 1 to 4 carbon atoms, such as a methyl, ethyl, *iso* - propyl or *tert* - butyl group, for example, a 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

The term "halogen" used herein means

fluorine, chlorine, bromine or iodine, preferably chlorine or bromine.

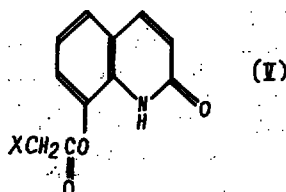
The compounds of the present invention represented by the formula (I) may be prepared from an 8 - hydroxycarbostryl according to the reaction scheme shown in the single Figure of the accompanying drawings.

The 8 - hydroxycarbostryl of the formula (VII) used as a starting material in the preparation of the compounds of the formula (IV) is a known compound and can easily be prepared by, for example, the method as disclosed in George R. Pettit *et al.*, *J. Org. Chem.*, 33, 1089 (1968).

As illustrated in the accompanying reaction scheme, the 5 - haloacetyl - 8 - hydroxycarbostryl represented by the formula (IV) which is an intermediate in the process of this invention can be prepared by one of the alternative routes (A), (B)+(B') or (C)+(C').

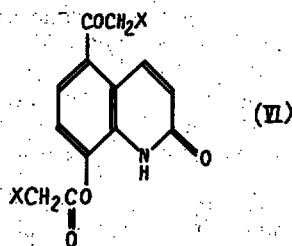
In the route (A), an 8 - hydroxycarbostryl of the formula (VII) is reacted with a haloacetyl halide in the presence or absence of a solvent and in the presence of a Lewis acid catalyst to form the 5 - haloacetyl - 8 - hydroxycarbostryl intermediate of the formula (IV) in one step.

In the route (B)+(B'), the reaction between the starting material (VII) and the haloacetyl halide results in the production of a 8 - haloacetoxycarbostryl of the formula (V)



wherein X is as defined above, which is then subjected to the rearrangement of the haloacetyl group to form the intermediate of the 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 - haloacetoxycarbostryl of the formula (VI)



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

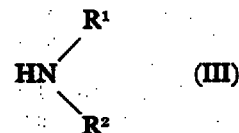
In practice, the reaction between the 8 - hydroxycarbostryl and the haloacetyl halide proceeds via a combination of the above-

described three reactions, i.e., (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 would be 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 would be a mixture of the compounds of the formulae (IV) and (VI) with a small amount of the compound of the formula (V).

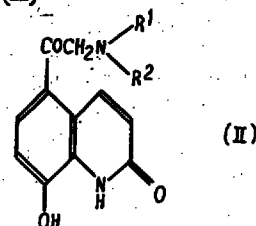
Isolation of the compound of the formula (IV), (V) or (VI) from the reaction product can be advantageously carried out by well known procedures, for example, by fractional crystallization.

In a preferred embodiment employing a solvent, after completion of the reaction, the solvent 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. The insoluble substances are recrystallized from methanol to obtain the 5 - haloacetyl - 8 - hydroxycarbostryl 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 the 8 - haloacetoxycarbostryl 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 the 5 - haloacetyl - 8 - haloacetoxycarbostryl of the formula (VI).

The thus-obtained 5 - haloacetyl - 8 - hydroxycarbostryl intermediate of the formula (IV) is then reacted with ammonia or a secondary or tertiary organic amine represented by the formula (III)



wherein R¹ and R² are as defined above, in the presence or absence of a solvent to obtain a novel 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative represented by the formula (II)



wherein R¹ and R² are as defined above.

(13)
4 The 5 - [1 - hydroxy - 2 - (substituted - amino)]ethyl - 8 - hydroxycarbostryl derivative of the formula (I) of the present invention can be prepared by reducing the above
5 obtained 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative of the formula (II).

Both the 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivatives of the
10 formula (II), an intermediate product of the present invention, and the final product, 5 - [1 - hydroxy - 2 - (substituted - amino)]ethyl - 8 - hydroxycarbostryl derivatives of the formula (I) are novel compounds. The
15 compounds of formula (II) form the subject of our copending Patent Application No. 29524/77, (Serial No. 1496872) of even date.

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

The haloacetyl halide which is used in the present invention as a reactant in the preparation of the compound of the formula (IV) includes those having a chlorine, bromine,
25 iodine or fluorine atom as the halogen atom, with chloroacetyl chloride being preferred.

In the reaction step (A), the catalyst may be a conventional Lewis acid, for example, aluminium chloride or bromide, zinc chloride,
30 ferric chloride, stannic chloride, titanium chloride or boron trifluoride, 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,
35 per mole of the 8 - hydroxycarbostryl.

This reaction can be effected in the absence of a solvent but the reaction proceeds more smoothly in an inert organic solvent. Suitable
40 examples of inert organic solvents which can be used in this reaction are carbon disulphide, nitrobenzene, diethyl ether and dioxane, carbon disulphide being preferred. These inert organic solvents are usually used in a volume of from 0.5 to 20, preferably from
45 2 to 10, times the volume of the reactants. The reaction is advantageously carried out under anhydrous conditions.

Reaction (A) is generally conducted using from an equimolar amount to a large excess
50 of the haloacetyl halide, preferably from 2 to 20 moles, most preferably from 2 to 10 moles, of the haloacetyl halide per mole of the 8 - hydroxycarbostryl of the formula (VII). The reaction may be conducted at a
55 temperature of 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,
60 preferably from 1 to 10 hours.

Reaction (B) may be carried out using the same amount of the same catalyst as used in reaction (A) in the same solvent as used
65 in reaction (A) or in the absence of a solvent. This reaction may 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 - hydroxycarbostryl of the formula (VII) at a temperature of
70 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 - hydroxycarbostryl of the formula (IV) from the 8 - haloacetoxycarbostryl of the
75 formula (V) obtained in reaction (B) as above described is generally known as a Fries rearrangement, and can be carried out using the same amount of the same catalyst as in reaction (A) in the same solvent as in reaction (A) or in the absence of any solvent. The
80 reaction temperature may be from room temperature to 150°C, preferably from room temperature to 80°C and the reaction time may be from 1 to 20, preferably from 1 to 10 hours. This reaction may proceed in the
85 presence of any haloacetyl halide which remains unreacted in the previous reaction system (B). In such a case, it has been found that the presence of the haloacetyl halide improves the yield of the product, the 5 - haloacetyl - 8 - hydroxycarbostryl of the formula (IV).
90

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 in the absence of
95 any solvent. The haloacetyl halide may be used in from an equimolar amount to a large excess, but preferably in an amount of from 2 to 20 moles, preferably from 2 to 10 moles, per mole of the 8 - hydroxycarbostryl of the formula (VII). The reaction temperature may be from room temperature to 150°C,
100 preferably from room temperature to 80°C, and the reaction time may be from 1 to 20 hours, preferably 1 to 10 hours.

Reaction (C') to obtain the compound of the formula (IV) from the above-obtained 5 -
110 haloacetyl - 8 - haloacetoxycarbostryl of formula (VI) may be conducted using a catalyst, for example, a basic substance such as an alkali metal hydroxide or carbonate, e.g., sodium hydroxide, potassium hydroxide,
115 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
120 isopropanol. The amount of the catalyst varies depending upon the type of catalyst used. For example, hydrochloric acid or sodium hydroxide may be used in an amount of from 1 to 5 moles per mole of the 5 -
125 haloacetyl - 8 - haloacetoxycarbostryl of the formula (VI). The reaction generally proceeds at a temperature of from 0° to 150°C for from 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 can be used as a reactant in the preparation of the 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative of the formula (II) 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 - hydroxycarbostryl intermediate of the formula (IV) and the amine of the formula (III) can be carried out in the absence of a solvent since the amine reactant itself 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 a 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 - hydroxycarbostryl of the formula (IV) at from room temperature to the refluxing temperature of the reaction system, preferably from 40° to 100°C at from atmospheric pressure to 10 atmospheres.

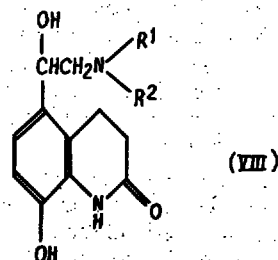
The reduction of the above obtained 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative of the formula (II) to a 5 - [1 - hydroxy - 2 - (substituted - amino)]ethyl - 8 - hydroxycarbostryl derivative of the formula (I) may be conducted using a reducing agent such as lithium aluminium hydride, or sodium borohydride or in the presence of a catalyst such as palladium black, platinum oxide, palladium-on-carbon, Raney nickel or platinum black 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 carbostryl 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 alcohols such as methanol, ethanol and propanols, 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.

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

The compounds of the present invention represented by the formula (I) wherein R¹ and R² represent hydrogen atoms can also be prepared from the compounds of the formula (II) wherein either R¹ or R² represents a benzyl group or an α - methylbenzyl group. The above benzyl or α - methylbenzyl group can easily be split off during the catalytic reduction to produce the compounds of the present invention wherein R¹ and R² are hydrogen atoms.

The compounds of the present invention represented by the formula (I) can also be prepared by dehydrogenating the corresponding 3,4 - dihydrocarbostryl derivatives of the formula (VIII)



wherein R¹ and R² are as described above, which are disclosed in our copending Patent Application No. 55899/74, (Serial No. 1496768) of even date.

The dehydrogenation can be conducted by any known procedure which is capable of releasing a hydrogen atom from each of the 3- and 4-positions of the carbostryl moiety

to form a double bond between the 3- and 4-positions. This dehydrogenation can 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, platinum oxide or Raney nickel; or (3) a procedure using a dehydrogenating agent such as sulphur or selenium dioxide, advantageously using the above procedure (1) or (2). The dehydrogenation can be carried out in a solvent such as an aromatic hydrocarbon, for example, benzene, toluene, xylene, phenetol or chlorobenzene; a lower alcohol, for example, methanol, ethanol, *iso* - propanol or *tert* - butanol, an ether, for example, dioxane; a ketone, 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 for a period of from 10 to 30 hours. The dehydrogenation agent is generally used in an amount of from 1 to 5 moles per mole of the 3,4 - dihydrocarbostyryl of the formula (VIII), and the metal catalyst is generally used in an amount of 0.5 to 3 moles per mole of the 3,4 - dihydrocarbostyryl of the formula (VIII).

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 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 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 the acid addition salts thereof exhibit a stimulating activity on β - adreno - receptor and, therefore, are very useful as pharmaceuticals for treating disorders such as bronchial asthma.

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 - hydroxycarbostyryl

5 - (1 - Hydroxy - 2 - *sec* - butylamino) - ethyl - 8 - hydroxycarbostyryl 65
 5 - (1 - Hydroxy - 2 - *tert* - butylamino) - ethyl - 8 - hydroxycarbostyryl
 5 - [1 - Hydroxy - 2 - (α - methylbenzylamino)]ethyl - 8 - hydroxycarbostyryl
 5 - [1 - Hydroxy - 2 - (α, α - dimethylphenethylamino)]ethyl - 8 - hydroxycarbostyryl 70
 5 - (1 - Hydroxy - 2 - piperidino)ethyl - 8 - hydroxycarbostyryl
 5 - (1 - Hydroxy - 2 - morpholino)ethyl - 8 - hydroxycarbostyryl 75
 5 - (1 - Hydroxy - 2 - benzylamino)ethyl - 8 - hydroxycarbostyryl
 5 - [1 - Hydroxy - 2 - (1 - phenethylamino)]ethyl - 8 - hydroxycarbostyryl 80
 5 - (1 - Hydroxy - 2 - amino)ethyl - 8 - hydroxycarbostyryl.

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. 85

The present invention is further illustrated in greater detail by reference to the following Examples, which are given for illustrative purposes only and are not to be construed as limiting the scope of the invention. Unless otherwise indicated, all parts, percentages, ratios and the like are by weight. 90 95

EXAMPLE 1

27 Grams of 8 - hydroxycarbostyryl (VII) and 37 ml of chloroacetyl chloride were dissolved in 250 ml of nitrobenzene, and to the resulting solution were added 85 g of aluminium chloride. The mixture was then stirred at 70°C for 20 hours. 500 ml of 10% aqueous hydrochloric acid were added to the reaction mixture and the nitrobenzene was removed by steam distillation. After cooling the mixture, the precipitated crystals were collected by filtration and were then washed with 300 ml of hot water. Recrystallization from methanol gave 14.0 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—287°C (with decomposition) as pale yellow crystals. 100 105 110

EXAMPLE 2

20 Grams of aluminium chloride were added to 5.0 g of 8 - hydroxycarbostyryl (VII) and the resulting mixture was thoroughly mixed. 10 g of chloroacetyl chloride were gradually added to the mixture while ice-cooling. The mixture was allowed to react by heating it at 40° to 45°C for 2 hours to form 8 - chloroacetoxycarbostyryl (V) and then stirred at 70°C for 3 hours. After cooling, the precipitated crystals were collected by filtration, and the crystals were washed with 300 ml of water followed by recrystallization from methanol to obtain 2.6 g 115 120 125

of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—287°C (with decomposition) as pale yellow crystals.

On the other hand, a part of the 8 - chloroacetoxycarbostyryl (V) which had been formed in this example was removed and recrystallized from acetone to give pale yellow crystals. The melting point of these crystals was found to be 248—250°C (with decomposition).

EXAMPLE 3

1.5 Grams of chloroacetyl chloride and 20 ml of carbon disulphide were added to 0.5 g of 8 - hydroxycarbostyryl (VII), and 2 g of aluminium chloride were gradually added to the resulting solution while ice-cooling. After thorough stirring, the mixture was gradually heated and refluxed for 30 minutes. After cooling, the unreacted chloroacetyl chloride and the carbon disulphide were removed, and crushed ice was added to the resulting residue to crystallize the product. The crystals thus obtained were washed with water and then recrystallized from acetone to obtain 0.45 g of 8 - chloroacetoxycarbostyryl (V) having a melting point of 248—251°C (with decomposition) as pale yellow crystals.

EXAMPLE 4

20 Grams of aluminium chloride and 10 g of chloroacetyl chloride were added to 10 g of the 8 - chloroacetoxycarbostyryl (V) obtained in Example 3, and the resulting mixture was heated at 75 to 85°C for 1 hour. The mixture was poured onto crushed ice while warm and the precipitated crystals were filtered, washed with water and recrystallized from methanol to obtain 3.7 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—287°C (with decomposition) as pale yellow crystals.

EXAMPLE 5

7.3 Grams of 8 - hydroxycarbostyryl (VII) and 12.5 g of chloroacetyl chloride were added to 70 ml of nitrobenzene, and 30 g of aluminium chloride were gradually added to the resulting solution while stirring under ice-cooling. The mixture was stirred at 50 to 55°C for 6 hours and then poured into ice-water. The precipitated crystals were filtered, washed with methanol and recrystallized from acetone to obtain 3.5 g of 5 - chloroacetyl - 8 - chloroacetoxycarbostyryl (VI) having a melting point of 239—241°C (with decomposition) as pale yellow crystals.

EXAMPLE 6

1.7 Grams of the 5 - chloroacetyl - 8 - chloroacetoxycarbostyryl (VI) obtained in Example 5 were added to 50 ml of 10% aqueous hydrochloric acid followed by stirring at 95 to 100°C for 2 hours. After

cooling, the precipitated crystals were filtered, washed with water and then recrystallized from methanol to obtain 1.1 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—286°C (with decomposition) as pale yellow crystals.

EXAMPLE 7

2.5 Grams of the 5 - chloroacetyl - 8 - chloroacetoxycarbostyryl (VI) obtained in Example 5 were added to 30 ml of 5% aqueous potassium hydroxide and the mixture was then stirred at 20 to 25°C for 30 minutes. The resulting solution was adjusted to a pH of 2 to 3 with dilute hydrochloric acid and was cooled. The precipitated crystals were filtered, washed with water and recrystallized from methanol to obtain 1.7 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—287°C (with decomposition) as pale yellow crystals.

EXAMPLE 8

20 Grams of aluminium chloride were gradually added to a mixture of 4.5 g of 8 - hydroxycarbostyryl and 10 g of chloroacetyl chloride while stirring under ice-cooling. The resulting mixture was stirred at 55 to 60°C for 8 hours to form 5 - chloroacetyl - 8 - chloroacetoxycarbostyryl. 40 ml of 5% potassium hydroxide were then added to the reaction mixture which was then stirred at room temperature for 30 minutes. A 10% aqueous hydrochloric acid solution was added thereto to make the solution acidic and to form crystals. The precipitated crystals were filtered, washed with water and then recrystallized from methanol to obtain 2.3 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) having a melting point of 285—286°C (with decomposition) as pale yellow crystals.

On the other hand, a part of the above reaction mixture before the addition of the 5% aqueous potassium hydroxide as described above was taken out and poured into ice-water. The precipitated crystals were filtered, washed with methanol and recrystallized from ethyl acetate to obtain 5 - chloroacetyl - 8 - chloroacetoxycarbostyryl (VI) having a melting point of 238—241°C (with decomposition) as pale yellow crystals.

EXAMPLE 9

12.6 Grams of the 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) obtained in Example 4 or 8 were suspended in 130 ml of iso - propanol, and 2515 g of iso - propylamine (III) were added dropwise to the resulting suspension while stirring. The reaction mixture was then stirred at 55 to 60°C for 3 hours. After cooling concentrated hydrochloric acid was added to the mixture to adjust the mixture to a pH of 2 to 3, and the precipitated crystals were filtered, washed with acetone and recrystallized from methanol-

dimethylformamide (1:1 by volume) to obtain 6.5 g of 5 - *iso* - propylaminoacetyl - 8 - hydroxycarbostyryl (II) hydrochloride having a melting point of 286—288°C (with decomposition) as pale yellow crystals.

EXAMPLE 10

8.0 Grams of the 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) obtained in Example 4 or 8 were suspended in 100 ml of ethanol, and 10 g of *tert* - butylamine were added dropwise to the resulting suspension while stirring. The mixture was then stirred at 55 to 60°C for 5 hours. After the mixture had been concentrated to half the volume, concentrated hydrochloric acid was added thereto to adjust the mixture to a pH of 2 to 3. The precipitated crystals were filtered, washed with acetone and recrystallized from ethanol to obtain 4.1 g of 5 - *tert* - butylaminoacetyl - 8 - hydroxycarbostyryl (II) having a melting point of 291—293°C (with decomposition) as pale yellow crystals.

EXAMPLE 11

4.3 Grams of the 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) obtained in Example 4 or 8 were suspended in 50 ml of ethanol, and 5 g of *sec* - butylamine were added dropwise to the resulting suspension while stirring. The mixture was then stirred at 60 to 65°C for 5 hours. After cooling, the resulting mixture was adjusted to a pH of 3 with concentrated hydrochloric acid. The precipitated crystals were filtered, washed with acetone and recrystallized from methanol-ethanol (1:1 by volume) to obtain 2.9 g of 5 - *sec* - butylaminoacetyl - 8 - hydroxycarbostyryl (II) hydrochloride having a melting point of 289—291°C (with decomposition) as pale yellow crystals.

EXAMPLE 12

10 Grams of the 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) prepared in Example 4 or 8 were suspended in 50 ml of benzene, and 10 ml of piperidine (III) were added to the suspension. The mixture was then heated under reflux and stirring for 6 hours. The reaction mixture was filtered to recover the reaction product which was then washed with benzene and then with 50 ml of *iso* - propanol. The resulting insoluble material was dissolved in 150 ml of a 2% aqueous hydrochloric acid. The solution was concentrated to dryness under reduced pressure and the resulting residue was recrystallized from ethanol to obtain 7.5 g of white amorphous 5 - piperidinoacetyl - 8 - hydroxycarbostyryl (II) hydrochloride 1/2 hydrate having a melting point of 239—241°C (with decomposition).

EXAMPLE 13

10 Grams of the 5 - chloroacetyl - 8 -

hydroxycarbostyryl (IV) prepared in Example 4 or 8 were suspended in 60 ml of benzene, and 9 ml of morpholine were added to the suspension. The mixture was then while heated under reflux and stirring for 4 hours. The reaction mixture was cooled and the resulting precipitate was filtered. The precipitate was dissolved in 60 ml of *iso* - propanol and the solution was adjusted to a pH of 2—3 with concentrated hydrochloric acid. The resulting acidic solution was cooled with ice and the precipitate formed was filtered followed by recrystallization from ethanol. The precipitate was dissolved in 20 ml of water and the solution was adjusted to a pH 7.5—8.0 with sodium bicarbonate and ice-cooled. The precipitate formed upon cooling was filtered and recrystallized from ethanol to obtain 4.2 g of white amorphous 5 - morpholinoacetyl - 8 - hydroxycarbostyryl (II) having a melting point of 238—239.5°C (with decomposition). The product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 14

120 Millilitres of benzylamine were added to 15 g of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) prepared as described in Example 4 or 8, and the mixture was stirred for one hour at room temperature. The precipitate which formed upon addition of petroleum ether to the reaction mixture was dissolved by addition of dilute hydrochloric acid and the solution was filtered to remove any remaining insoluble material. The hydrochloric acid layer was then concentrated to dryness, and the residue was recrystallized from methanol to obtain 16.4 g of a material having a melting point of 274—279°C (with colouring and decomposition). The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as 5 - benzylaminoacetyl - 8 - hydroxycarbostyryl (II) hydrochloride monohydrate.

EXAMPLE 15

10 Grams of 5 - chloroacetyl - 8 - hydroxycarbostyryl (IV) were dissolved in 50 ml of ethanol, and then 25 g of 1 - phenethylamine were added dropwise to the solution which was stirred at a temperature of 50°C for 4 hours. The ethanol was then distilled off, and the precipitate was washed with diethyl ether and dissolved in *iso* - propanol to remove any insoluble material. The *iso* - propanol layer was concentrated to a volume of about 1/3 the original volume and adjusted to a pH of 4 with concentrated hydrochloric acid. The precipitate formed was recrystallized from a mixture of ethanol and acetone to obtain 9.8 g of a material having a melting point of 246—249°C. The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as

5 - (1 - phenethylaminoacetyl) - 8 - hydroxycarbo-
styryl (II) hydrochloride.

EXAMPLE 16

40 Millilitres of 1,1 - dimethylphenethyl-
amine were added to 5 g of 5 - chloroacetyl -
8 - hydroxycarbo-
styryl, and the mixture was
stirred at room temperature in the dark for
5 hours. The precipitate which was formed
upon addition of petroleum ether to the
reaction mixture was washed with diethyl
ether and dissolved in a methanolic solution
of hydrochloric acid to remove any insoluble
material. The methanol was then distilled
off, and the residue was recrystallized from
methanol to obtain 6.1 g of a material having
a melting point of 246—247°C (with colour-
ing and decomposition). The product thus
obtained was confirmed by NMR and IR
spectral analyses as 5 - (1,1 - dimethyl-
phenethylaminoacetyl) - 8 - hydroxycarbo-
styryl hydrochloride 1/2 hydrate.

EXAMPLE 17

1.0 Gram of the 5 - iso - propylamino-
acetyl - 8 - hydroxycarbo-
styryl (II) hydro-
chloride obtained as described in Example 9
was dissolved in 40 ml of water, and 0.5 g
of palladium-on-carbon was added to the
resulting solution as a catalyst. The resulting
mixture was heated to 35 to 40°C while
stirring to absorb the hydrogen. Upon com-
pletion of the reduction reaction, the catalyst
was filtered, and the filtrate was concentrated
to dryness under reduced pressure. Ethanol
was added to the residue and then repeatedly
concentrated to dryness to completely remove
the water. The residue was crystallized from
acetone and recrystallized from ethanol -
acetone (1:1 by volume) to obtain 0.4 g of
pale yellow amorphous 5 - (1 - hydroxy - 2 -
iso - propylamino)ethyl - 8 - hydroxy-
carbo-
styryl (I) hydrochloride having a melting
point of 210—212°C (with decomposition).

EXAMPLE 18

2.0 Grams of the free base of the 5 - sec -
butylaminoacetyl - 8 - hydroxycarbo-
styryl (II) obtained as described in Example 11 were
dissolved in 100 ml of methanol, and 0.8 g
of sodium borohydride was gradually added
to the resulting solution while stirring under
cooling. The resulting mixture was stirred at
that temperature for 15 minutes and then at
room temperature for another 1 hour. Con-
centrated hydrochloric acid was added to the
mixture to adjust the mixture to a pH of
1.5 to 2, and the solvent was removed by
distillation under reduced pressure. To the
residue were added 30 ml of ethanol, and
then the mixture was concentrated to dryness
under reduced pressure to remove water. The
residue was dissolved in 50 ml of absolute
ethanol, and an ethanolic solution of sodium
hydroxide was added to the resulting solution

to adjust the solution to a pH of 7 to 8.5.
The precipitates thus formed were filtered,
and the filtrate was concentrated to dryness
under reduced pressure. The residue was
then extracted with 50 ml of absolute ethanol,
and hydrogen chloride was bubbled through
the extract. The extract was concentrated to
dryness under reduced pressure, and the
residue was recrystallized from iso - propyl
alcohol to obtain 1.3 g of pale yellow
amorphous 5 - (1 - hydroxy - 2 - sec -
butylamino)ethyl - 8 - hydroxycarbo-
styryl di-
hydrochloride monohydrate having a melting
point of 143—144°C (with decomposition).

EXAMPLE 19

1.5 Grams of the 5 - tert - butylamino-
acetyl - 8 - hydroxycarbo-
styryl (II) obtained
as described in Example 10 were dissolved
in 100 ml of methanol, and 0.7 g of sodium
borohydride was slowly added to the resulting
solution while stirring under cooling. The
stirring was further continued at that tem-
perature for 15 minutes and at room tem-
perature for an additional hour. The reaction
product was worked up in the same manner
as described in Example 18 and then recrystal-
lized from ethanol to obtain 0.9 g of pale
yellow amorphous 5 - (1 - hydroxy - 2 -
tert - butylamino)ethyl - 8 - hydroxycarbo-
styryl hydrochloride having a melting point
of 242—244°C (with decomposition).

EXAMPLE 20

2.0 Grams of 5 - piperidinoacetyl - 8 -
hydroxycarbo-
styryl (II) hydrochloride prepared
as described in Example 12 were dissolved
in 200 ml of methanol, and 2.0 g of sodium
borohydride were added to the solution while
ice-cooling. The mixture was then stirred
for 2 hours. The mixture was adjusted to a
pH of 2 to 3 with concentrated hydrochloric
acid, and the mixture was allowed to stand
for one hour at room temperature followed
by filtration. The filtered reaction mixture
was concentrated under reduced pressure, and
the residue was dissolved in 30 ml of ethanol.
The solution was filtered to remove any
insoluble material, and the filtrate was con-
centrated under reduced pressure. These pro-
cedures (dissolution in ethanol, filtration and
concentration) were repeated three times. The
resulting residue was dissolved in acetone
by heating and the precipitate formed upon
cooling was filtered and recrystallized from
iso - propanol to obtain 0.6 g of white
amorphous 5 - (1 - hydroxy - 2 - piperidino)-
ethyl - 8 - hydroxycarbo-
styryl hydrochloride
1 1/2 hydrate having a melting point of
146—148°C (with decomposition). The pro-
duct thus obtained was confirmed by IR and
NMR spectral analyses and elemental analysis.

EXAMPLE 21

1.0 Gram of 5 - morpholinoacetyl - 8 -

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hydroxycarbostyryl (II) prepared as in Example 13 was dissolved in 100 ml of methanol, and 1.2 g of sodium borohydride were added to the solution. The mixture was reacted for 2 hours while stirring. The reaction mixture was adjusted to a pH of 2—3 with concentrated hydrochloric acid and the mixture was allowed to stand at room temperature for one hour. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 ml of ethanol and the solution was filtered to remove any insoluble material followed by concentration of the filtrate under reduced pressure. These procedures (dissolution in ethanol, filtration and concentration) were repeated three times, and the residue thus obtained was crystallized from acetone. The precipitated crystals were filtered and triturated with 20 ml of an aqueous sodium bicarbonate solution to remove any soluble material by filtration, and the insoluble material was washed with water and dissolved in ethanol by heating. The resulting solution was adjusted to a pH of 2—3 with concentrated hydrochloric acid, and the precipitate formed upon cooling was filtered to obtain 0.6 g of white amorphous 5 - (1 - hydroxy - 2 - morpholino)ethyl - 8 - hydroxycarbostyryl (I) hydrochloride 1 1/2 hydrate having a melting point of 157—158.5°C (with decomposition). The product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 22

50 Millilitres of methanol were added to 5 g of the free base of the 5 - benzylaminoacetyl - 8 - hydroxycarbostyryl (II) prepared as in Example 14, and 3 g of sodium borohydride were added slowly to the solution under ice-cooling and stirring. The mixture was then stirred at room temperature for one hour. The resulting 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 crystallized from acetone. The resulting crystals were adjusted to a pH 8 with an aqueous sodium hydroxide solution, the precipitate formed was filtered and washed with water. The precipitate was adjusted to a pH of 1 with dilute hydrochloric acid and concentrated to dryness. The residue thus obtained was recrystallized from a mixture of methanol and acetone to obtain 4.2 g of a white amorphous material having a melting point of 120—121°C. The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as 5 - (1 - hydroxy - 2 - benzylamino)ethyl - 8 - hydroxycarbostyryl (I) hydrochloride dihydrate.

EXAMPLE 23

1 Gram of 5 - (1 - phenethylaminoacetyl) - 8 - hydroxycarbostyryl (II) hydrochloride prepared as described in Example 15 was dissolved in 50 ml of methanol, and the solution was rendered weakly alkaline with a methanolic solution of sodium hydroxide. 0.5 g of sodium borohydride was then added slowly to the mixture while ice-cooling and the mixture was then stirred at room temperature for one hour. The precipitate which was formed upon addition of concentrated hydrochloric acid to adjust the pH to 3 was filtered, and the filtrate was concentrated to dryness. The resulting residue was dissolved in absolute ethanol and the solution was adjusted to a pH of 9 with an ethanolic solution of sodium hydroxide. The precipitate was filtered, and the filtrate was concentrated to dryness. The residue was crystallized from acetone and washed with water. The resulting crystals were dissolved in *iso* - propanol and the solution was saturated with hydrogen chloride gas followed by cooling. The precipitate formed was filtered and recrystallized from *iso* - propanol to obtain 0.77 g of a white amorphous material having a melting point of 162—164°C. The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as 5 - [1 - hydroxy - 2 - (1 - phenethylamino)] - ethyl - 8 - hydroxycarbostyryl (I) hydrochloride dihydrate.

EXAMPLE 24

0.1 Gram of platinum oxide and 50 ml of water were added to 0.5 g of 5 - benzylaminoacetyl - 8 - hydroxycarbostyryl (II) hydrochloride monohydrate prepared as described in Example 14, and the mixture was reduced at room temperature under atmospheric pressure in a hydrogen atmosphere for 24 hours while shaking. After completion of the reduction, the catalyst was filtered and the aqueous phase was concentrated to dryness. The residue was recrystallized from a mixture of methanol and acetone to obtain 0.25 g of a white amorphous 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxycarbostyryl (I) hydrochloride having a melting point of 261—262°C (with decomposition). The product thus obtained was confirmed by IR and NMR spectral analyses and elemental analysis.

EXAMPLE 25

1.5 Grams of 5 - (1,1 - dimethylphenethylaminoacetyl) - 8 - hydroxycarbostyryl (II) were dissolved in 50 ml of methanol, and 1 g of sodium borohydride was added slowly to the solution under ice-water cooling while stirring. The stirring was continued at room temperature for an additional hour. The resulting mixture was then adjusted to a pH of 1 with concentrated hydrochloric acid and

the mixture was concentrated to dryness. The residue was dissolved in ethanol and any insoluble material was removed by filtration. The ethanolic layer was concentrated to dryness and the residue was dissolved in *iso* - propanol. The *iso* - propanol layer was concentrated and acetone was added to crystallize the product. Recrystallization of the product from methanol - acetone yielded 1.4 g of a white amorphous material having a melting point of 167—168°C (with colouring and decomposition). The material thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis to be 5 - [2 - (1,1 - dimethylphenethylamino) - 1 - hydroxy]ethyl - 8 - hydroxycarbostryl (I) hydrochloride dihydrate.

EXAMPLE 26 •

2.5 Grams of chloranil and 20 ml of xylene were added to 2.2 g of 5 - (1 - hydroxy - 2 - amino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostryl (VIII), and the mixture was heated under refluxing for 24 hours. The reaction mixture was then concentrated to dryness and the residue was washed thoroughly with carbon tetrachloride. The residue was then dissolved in 30 ml of methanol and the solution was adjusted to a pH of 1 by introducing hydrogen chloride gas into the solution followed by cooling. The precipitated crystals were filtered and recrystallized from methanol to obtain 1.5 g of a material having a melting point of 261—262°C (with decomposition). The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as 5 - (1 - hydroxy - 2 - amino) - ethyl - 8 - hydroxycarbostryl (I) hydrochloride.

EXAMPLE 27

200 Millilitres of water, 0.9 g of sodium hydroxide and 4.3 g of Raney nickel were added to 4.3 g of 5 - [1 - hydroxy - 2 - (1,1 - dimethylphenethylamino)ethyl - 8 - hydroxy - 3,4 - dihydrocarbostryl (VIII) hydrochloride dihydrate, and the mixture was heated under refluxing at a temperature of 80°C for 15 hours. The reaction mixture was then filtered to remove the catalyst, and the filtrate was concentrated. The resulting precipitated crystals were recrystallized from water to obtain 2.6 g of a material having a

melting point of 167—168°C (with decomposition). The product thus obtained was confirmed by NMR and IR spectral analyses and elemental analysis as 5 - [1 - hydroxy - 2 - (1,1 - dimethylphenethylamino)]ethyl - 8 - hydroxycarbostryl (I) hydrochloride monohydrate.

In the same manner as described in Example 27, the following compound of the formula (I) was prepared:

5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostryl hydrochloride having a melting point of 210—212°C (with decomposition).

REFERENCE EXAMPLE

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

Male hybrid adult dogs, weighing 10 to 15 Kg were anaesthetized with 30 mg/Kg of body weight of sodium pentobarbital administered intravenously. Each of the anaesthetized dogs was secured on its back and a cannula was inserted into the trachea. Artificial respiration was conducted using a device according to the Konzett-Rössler method [Konzett H. & Rössler R., "Versuchsanordnung zu Untersuchungen an der Bronchial Moskolatur", *Arch. Exp. Path., Pharmacol.*, 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 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 condition constant over the test period. The results obtained are shown in Table I below.

TABLE I
Bronchial Resistance (%)

		Dosage Level ($\mu\text{g/Kg}$)								
Compound		0.01	0.03	0.1	0.3	1.0	3.0	10	30	100
5	5-(1-Hydroxy-2- <i>iso</i> -propyl-amino)ethyl-8-hydroxycarbostryl Hydrochloride	5.5	27.7	66.6	83.3	100	—	—	—	—
10	5-(1-Hydroxy-2- <i>tert</i> -butyl-amino)ethyl-8-hydroxycarbostryl Hydrochloride	7.3	35.5	78.6	90.4	100	—	—	—	—
	5-[1-Hydroxy-2-(α,α -dimethylphenethylamino)]-ethyl-8-hydroxycarbostryl Hydrochloride	3.3	20.0	47.5	87.8	100	—	—	—	—
15	(Control)	0	16.6	58.3	83.3	100	—	—	—	—
	Isoproterenol									
	Salbutamol	0	0	16.6	33.3	66.6	100	—	—	—
	Metaproterenol Sulfate (Arotec)	0	0	2.7	11.1	27.5	50.0	88.3	100	—
20	Quinterenol	0	0	0	0	0	0	0	7.6	15.3

Further, the acute toxicity was determined with respect to 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 a control. The LD_{50} (50% lethal dose) results are as follows.

TABLE II

		LD ₅₀ (mg/Kg)	
Compound		i.v.	p.o.
5	5-(1-Hydroxy-2- <i>iso</i> -propylamino)ethyl-8-hydroxycarbostyryl Hydrochloride	90 (70-115)	970 (441-2134)
	5-[1-Hydroxy-2-(α,α -dimethylphenethyl-amino)]ethyl-8-hydroxycarbostyryl Hydrochloride	102 (84.6-112.8)	2900 (2180-3560)
10	Salbutamol	57.1 (52.7-61.9)	4620* (4160-5130)*
			660 (412.5-1056)
15	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, inhalant (aerosol spray) or suppository, preferably, in combination with pharmaceutically acceptable carriers or diluents which 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 may contain other active components which do not adversely affect the activities of the compound of this invention.

Suitable pharmaceutical carriers or diluents include solid carriers such as corn starch, calcium sulphate dihydrate, magnesium stearate, lactose, and Aerosil (Registered Trade Mark of Nihon Aerosil Co., Ltd., Japan) which are suitable for use in oral, suppository, injectable and inhalant formulations. The oral dosage forms 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 as a 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
5 - (1 - hydroxy - 2 - <i>iso</i> - propylamino)ethyl - 8 - hydroxy - carbostyryl	1 mg
Corn Starch	70 mg
Magnesium stearate	9 mg
Lactose	20 mg
Total	100 mg

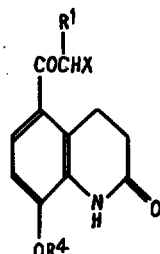
Formulation 2

An aerosol spray for inhalation containing the following components per dose was prepared and placed in an aerosol dispenser:

5	Components	Amount
	5 - (1 - hydroxy - 2 - <i>iso</i> - propylamino)ethyl - 8 - hydroxy - carbostyryl	50 mcg
	Oleic Acid	10 mcg
10	Dichlorodifluoromethane	57 mg
	Trichlorofluoromethane	25 mg

WHAT WE CLAIM IS:—

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



(I)

wherein R¹ and R², which may be the same or different, each represents a hydrogen atom or 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 R¹ and R² 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 R¹ and R² each represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

3. A derivative according to Claim 1, wherein R¹ represents a hydrogen atom and R² represents a phenylalkyl group.

4. A derivative according to Claim 3, wherein R² represents a benzyl, α - methylbenzyl, α, α - dimethylbenzyl, phenethyl or α, α - dimethylphenethyl group.

5. A derivative according to Claim 1, wherein R¹ and R², together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5- or 6-membered heterocyclic ring optionally containing an oxygen or sulphur atom and which may be unsubstituted or alkyl substituted.

6. A derivative according to Claim 5, wherein said heterocyclic ring is a pyrrolidino, piperidino, morpholino, piperazino, 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

7. 5 - (1 - Hydroxy - 2 - *iso* - propylamino)ethyl - 8 - hydroxycarbostyryl.

8. 5 - (1 - Hydroxy - 2 - *sec* - butylamino)ethyl - 8 - hydroxycarbostyryl. 55

9. 5 - (1 - Hydroxy - 2 - *tert* - butylamino)ethyl - 8 - hydroxycarbostyryl.

10. 5 - [1 - Hydroxy - 2 - (α - methylbenzylamino)]ethyl - 8 - hydroxycarbostyryl. 60

11. 5 - [1 - Hydroxy - 2 - (α, α - dimethylphenethylamino)]ethyl - 8 - hydroxycarbostyryl.

12. 5 - (1 - Hydroxy - 2 - piperidino)ethyl - 8 - hydroxycarbostyryl. 65

13. 5 - (1 - Hydroxy - 2 - morpholino)ethyl - 8 - hydroxycarbostyryl.

14. 5 - (1 - Hydroxy - 2 - benzylamino)ethyl - 8 - hydroxycarbostyryl.

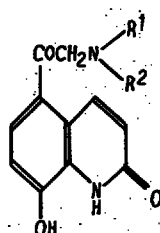
15. 5 - [1 - Hydroxy - 2 - (1 - phenethylamino)]ethyl - 8 - hydroxycarbostyryl. 70

16. 5 - (1 - Hydroxy - 2 - amino)ethyl - 8 - hydroxycarbostyryl.

17. An acid addition salt of an 8 - hydroxycarbostyryl derivative as claimed in any preceding Claim. 75

18. An acid addition salt according to Claim 17, which is a hydrochloride, a sulphate, a phosphate, a maleate, a fumarate or an oxalate. 80

19. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyryl derivative of the general formula (I) defined in any of Claims 1 to 6 or an acid addition salt thereof, which comprises reducing a 5 - substituted - aminoacetyl - 8 - hydroxycarbostyryl derivative represented by the following general formula (II):



(II)

wherein R¹ and R² are as defined in any of Claims 1 to 6 or an acid addition salt thereof, with hydrogen in the presence of a catalyst or with a reducing agent.

20. A process according to Claim 19, wherein the reduction is effected by using palladium black, palladium - on - carbon, platinum oxide or Raney nickel as a catalyst in an amount of from 0.05 to 1 mole per mole of said 5 - substituted - aminoacetyl - 8 - hydroxycarbostyryl 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. 100

21. A process according to Claim 20, wherein the catalyst is used in an amount

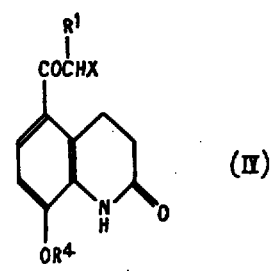
Formulation 2

An aerosol spray for inhalation containing the following components per dose was prepared and placed in an aerosol dispenser:

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

WHAT WE CLAIM IS:—

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



wherein R¹ and R², which may be the same or different, each represents a hydrogen atom or 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 R¹ and R² 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 R¹ and R² each represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

3. A derivative according to Claim 1, wherein R¹ represents a hydrogen atom and R² represents a phenylalkyl group.

4. A derivative according to Claim 3, wherein R² represents a benzyl, α - methylbenzyl, α,α - dimethylbenzyl, phenethyl or α,α - dimethylphenethyl group.

5. A derivative according to Claim 1, wherein R¹ and R², together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5- or 6-membered heterocyclic ring optionally containing an oxygen or sulphur atom and which may be unsubstituted or alkyl substituted.

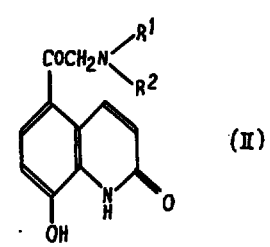
6. A derivative according to Claim 5, wherein said heterocyclic ring is a pyrrolidino, piperidino, morpholino, piperazino, 2 - methylpiperidino, 3 - methylpiperidino or N - methylpiperazino group.

7. 5 - (1 - Hydroxy - 2 - iso - propylamino)ethyl - 8 - hydroxycarbostyryl.
8. 5 - (1 - Hydroxy - 2 - sec - butylamino)ethyl - 8 - hydroxycarbostyryl.
9. 5 - (1 - Hydroxy - 2 - tert - butylamino)ethyl - 8 - hydroxycarbostyryl.
10. 5 - [1 - Hydroxy - 2 - (α - methylbenzylamino)]ethyl - 8 - hydroxycarbostyryl.
11. 5 - [1 - Hydroxy - 2 - (α,α - dimethylphenethylamino)]ethyl - 8 - hydroxycarbostyryl.
12. 5 - (1 - Hydroxy - 2 - piperidino)ethyl - 8 - hydroxycarbostyryl.
13. 5 - (1 - Hydroxy - 2 - morpholino)ethyl - 8 - hydroxycarbostyryl.
14. 5 - (1 - Hydroxy - 2 - benzylamino)ethyl - 8 - hydroxycarbostyryl.
15. 5 - [1 - Hydroxy - 2 - (1 - phenethylamino)]ethyl - 8 - hydroxycarbostyryl.
16. 5 - (1 - Hydroxy - 2 - amino)ethyl - 8 - hydroxycarbostyryl.

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

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

19. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyryl derivative of the general formula (I) defined in any of Claims 1 to 6 or an acid addition salt thereof, which comprises reducing a 5 - substituted - aminoacetyl - 8 - hydroxycarbostyryl derivative represented by the following general formula (II):



wherein R¹ and R² are as defined in any of Claims 1 to 6 or an acid addition salt thereof, with hydrogen in the presence of a catalyst or with a reducing agent.

20. A process according to Claim 19, wherein the reduction is effected by using palladium black, palladium - on - carbon, platinum oxide or Raney nickel as a catalyst in an amount of from 0.05 to 1 mole per mole of said 5 - substituted - aminoacetyl - 8 - hydroxycarbostyryl 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.

21. A process according to Claim 20, wherein the catalyst is used in an amount



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of from 0.1 to 0.5 mole per mole of said 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative.

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

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

24. A process according to any of Claims 19 to 23, wherein the reduction is effected in the presence of water or methanol ethanol or iso - propanol as a solvent.

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

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

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

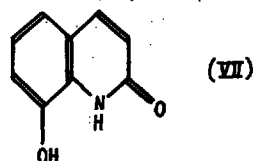
28. A process according to any of Claims 25 to 27, wherein lithium aluminium hydride is employed as the reducing agent and the reduction is effected in the presence of anhydrous ethyl ether, ethyl acetate or tetrahydrofuran as a solvent.

29. A process according to any of Claims 25 to 27, wherein sodium borohydride is employed as the reducing agent and the reduction is effected in the presence of water or methanol, ethanol, n - propanol or iso - propanol as a solvent.

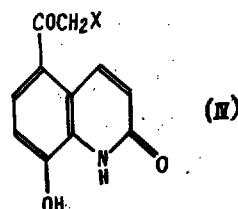
30. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostryl derivative of the general formula (I) defined in Claim 1, or an acid addition salt thereof, substantially as hereinbefore described with reference to any one of the foregoing Examples 17 to 25.

31. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostryl derivative of the general formula (I) defined in any of Claims 1 to 6 or an acid addition salt thereof, which comprises the steps of

(1) reacting 8 - hydroxycarbostryl represented by the following formula (VII):

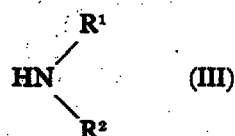


and a haloacetyl halide in the presence or absence of a solvent and in the presence of a Lewis acid catalyst to prepare a 5 - haloacetyl - 8 - hydroxycarbostryl derivative represented by the following general formula (IV):

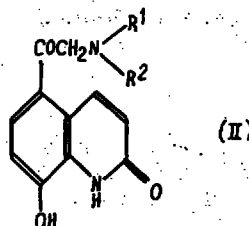


wherein X represents a halogen atom,

(2) reacting the resulting 5 - haloacetyl - 8 - hydroxycarbostryl derivative represented by the formula (IV) with ammonia or an amine represented by the following general formula (III):



wherein R¹ and R² are as defined in any of Claims 1 to 6 in the presence or absence of a solvent to prepare a 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative represented by the following general formula (II):



wherein R¹ and R² are as defined in any of Claims 1 to 6; and

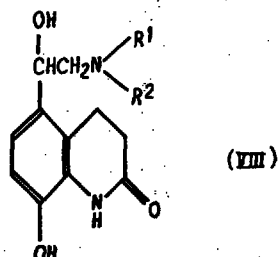
(3) reducing the resulting 5 - substituted - aminoacetyl - 8 - hydroxycarbostryl derivative represented by the general formula (II) or an acid addition salt thereof with hydrogen in the presence of a catalyst or with a reducing agent.

32. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostryl derivative of the general formula (I) defined in Claim 1 or an acid addition salt thereof, substantially as hereinbefore described.

33. A process for preparing a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostryl derivative of the



general formula (I) defined in any of Claims 1 to 6, or an acid addition salt thereof, which comprises dehydrogenating a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxy - 3,4 - dihydrocarbostyryl derivative of the following general formula (VIII):



wherein R¹ and R² are as defined in any of Claims 1 to 6, or an acid addition salt thereof.

34. A process according to Claim 33, wherein the dehydrogenation is effected by using as a dehydrogenating agent chloranil or dichlorodicyano - 1,4 - benzoquinone.

35. A process according to Claim 33, wherein the dehydrogenation is effected by using as a dehydrogenating agent selenium dioxide or sulphur.

36. A process according to Claim 34 or 35, wherein the dehydrogenating agent is employed in an amount of from 1 to 5 moles per mole of the 3,4 - dihydrocarbostyryl of formula (VIII).

37. A process according to Claim 33, wherein the dehydrogenation is effected by using a dehydrogenating metal catalyst.

38. A process according to Claim 37, wherein the catalyst comprises palladium black, platinum oxide or Raney nickel.

39. A process according to Claim 37 or 38, wherein the catalyst is employed in an amount of from 0.5 to 3 moles per mole of the 3,4 - dihydrocarbostyryl of the formula (VIII).

40. A process according to any of Claims 33 to 39, wherein the dehydrogenation is carried out in a solvent.

41. A process according to Claim 40, wherein the solvent is an aromatic hydrocarbon, a lower alcohol, an ether, a ketone, water or acetic acid.

42. A process according to Claim 40 or 41, wherein the dehydrogenation is effected at a temperature which is at or near the refluxing temperature of the reaction system.

43. A process according to any of Claims 40 to 42, wherein the dehydrogenation is effected for a period of from 10 to 30 hours.

44. A process for preparing a 5 - [1 -

hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyryl derivative according to Claim 1, substantially as hereinbefore described with reference to the foregoing Examples 26 or 27.

45. A 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyryl derivative according to Claim 1, when prepared by a process as claimed in any of Claims 19 to 44.

46. A pharmaceutical composition which comprises a 5 - [1 - hydroxy - 2 - (substituted - amino)] - ethyl - 8 - hydroxycarbostyryl derivative as claimed in any of Claims 1 to 18 or 45 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

47. A pharmaceutical composition according to Claim 46 and in a formulation suitable for inhalation in the form of an aerosol spray.

48. A pharmaceutical composition according to Claim 46 and in tablet form.

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

50. A pharmaceutical composition according to Claim 46 and substantially as hereinbefore described.

51. A method of stimulating the activity of β - adreno - receptor in a non-human by administering in said mammal a pharmaceutically-effective amount of a pharmaceutical composition as claimed in any of Claims 46 to 50.

52. A method of alleviating bronchial asthma in a non-human mammal, which comprises administering in said mammal a pharmaceutically-effective amount of a pharmaceutical composition as claimed in any of Claims 46 to 50.

53. A method of alleviating bronchial asthma in a non-human mammal, according to Claim 52 and substantially as hereinbefore described with reference to the foregoing Reference Example.

54. An aerosol dispenser containing a pharmaceutical composition as claimed in Claim 47.

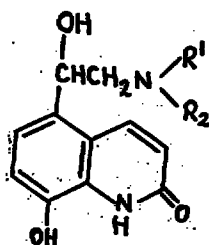
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ERRATUM

SPECIFICATION No. 1,496,769

Page 14, line 17, *delete existing formula insert*



(I)

THE PATENT OFFICE
3rd March, 1980