

PATENT SPECIFICATION

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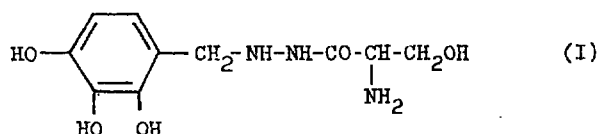


(54) NOVEL BENZYL-HYDRAZIDE DERIVATIVES AND A
 PROCESS FOR THE MANUFACTURE THEREOF AND NOVEL
 BENZYLIDENE-HYDRAZIDE DERIVATIVES USEFUL IN
 SAID PROCESS

(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—

The present invention is concerned with novel benzyl-hydrazide derivatives and a process for the manufacture thereof and with novel benzylidene-hydrazide derivatives useful in said process.

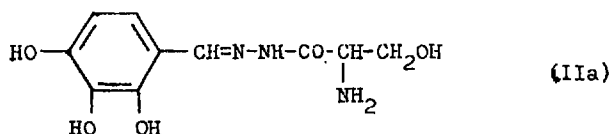
The novel benzyl-hydrazide derivatives provided by the invention are the compound of the formula



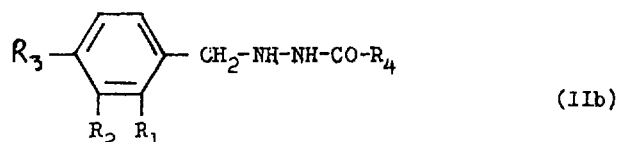
, which compound is derived from *L*-serine, and acid addition salts thereof.

The term "derived from *L*-serine" used in this specification denotes that the compound in question has a steric configuration corresponding to that of *L*-serine.

According to the process provided by the invention, the novel benzyl-hydrazide derivatives aforesaid are manufactured *either* by hydrogenating a benzylidene-hydrazide of the formula



, which is present in the form of the racemate or of the antipode derived from *L*-serine, or an acid addition salt thereof, or by converting in accordance with methods known *per se* the group or groups convertible into the hydroxy group and/or into the α -amino- β -hydroxyethyl group in a compound of the general formula



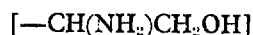
(19)

wherein R_1 , R_2 and R_3 signify hydroxy groups or-groups (as hereinafter defined) convertible into hydroxy groups and R_4 signifies the α -amino- β -hydroxyethyl group or a group (as hereinafter defined) convertible into the α -amino- β -hydroxyethyl group, at least one of the substituents R_1 , R_2 , R_3 and R_4 being different from the hydroxy group or from the α -amino- β -hydroxyethyl group, which compound is present in the form of the racemate or of the antipode derived from *L*-serine, or in an acid addition salt of such a compound, into the hydroxy group or into the α -amino- β -hydroxyethyl group, and isolating the antipode derived from *L*-serine from a racemate obtained, and, if desired, converting a base obtained into an acid addition salt.

It will be appreciated that the expression "methods known *per se*" is used in this description and in the accompanying claims to mean methods in actual use for or methods described in the literature on the subject.

The groups convertible into hydroxy groups designated in formula IIb by R_1 , R_2 and R_3 are benzyloxy groups, acetal groups which are derived from acetaldehyde, acetone or tetrahydropyran (e.g. α -methoxy-ethoxy, α -methoxy-isopropoxy and tetrahydropyranyloxy) or acyloxy groups (e.g. alkanoyloxy groups containing up to 4 carbon atoms), but are preferably benzyloxy groups. These groups can be converted into hydroxy groups in accordance with methods known *per se*; for example, the benzyloxy groups and the acetal groups can be converted into hydroxy groups by hydrogenolysis, preferably by means of catalytic hydrogenation (e.g. using noble-metal catalysts such as palladium and platinum catalysts), and the acyloxy groups can be converted into hydroxy groups by hydrolysis.

The groups convertible into the α -amino- β -hydroxyethyl group

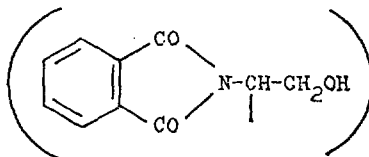


designated by R_4 in formula IIb are classified as follows:

- A) α -carbobenzoxylamino- β -hydroxyethyl ($C_6H_5-CH_2-OCONH-CH-CH_2OH$),
 α -benzylamino- β -hydroxyethyl ($C_6H_5-CH_2-NH-CH-CH_2OH$),
 α -benzylidencamino- β -hydroxyethyl ($C_6H_5-CH=N-CH-CH_2OH$),
 α -benzhydrylamino- β -hydroxyethyl [$(C_6H_5)_2CH-NH-CH-CH_2OH$],
 α -azido- β -hydroxyethyl ($N_3-CH-CH_2OH$),
 α -nitro- β -hydroxyethyl ($O_2N-CH-CH_2OH$),
 α -phenylazo- β -hydroxyethyl ($C_6H_5-N=N-CH-CH_2OH$),
 α -hydroximino- β -hydroxyethyl ($HON=C-CH_2OH$) and
 α -phenylhydrazono- β -hydroxyethyl ($C_6H_5-NH-N=C-CH_2OH$).

[These groups can be converted into the α -amino- β -hydroxyethyl group in accordance with methods known *per se*; for example, by hydrogenation. The hydrogenation can be effected catalytically using noble-metal catalysts such as palladium and platinum catalysts, or nickel or cobalt catalysts. These groups can also be converted into the α -amino- β -hydroxyethyl group by means of chemical reducing agents].

- B) α -formylamino- β -hydroxyethyl ($CHONH-CH-CH_2OH$),
 α -trifluoroacetyl amino- β -hydroxyethyl ($CF_3-CONH-CH-CH_2OH$),
 α -tritylamino- β -hydroxyethyl [$(C_6H_5)_3C-NH-CH-CH_2OH$],
 α -alkoxycarbonylamino- β -hydroxyethyl (alkyl-OCONH-CH-CH₂OH)
and
 α -phthalimido- β -hydroxyethyl



[These groups can be converted into the α -amino- β -hydroxyethyl groups by hydrolysis in accordance with methods known *per se*. Thus, the hydrolysis of the α -formylamino- β -hydroxyethyl group can be effected by means of dilute alcoholic hydrochloric acid, whereas the hydrolysis of the α -trifluoroacetyl amino- β -hydroxyethyl group may also be effected by means of a dilute aqueous ammonia solution. The conversion of the α -phthalimido- β -hydroxyethyl group into the α -amino- β -hydroxyethyl group can be effected by means of hydrazine.]

C) α -halo- β -hydroxyethyl (halogen-CH-CH₂OH),

α -alkylsulfonyloxy- β -hydroxyethyl (alkyl-SO₂O-CH-CH₂OH) and

α -arylsulfonyloxy- β -hydroxyethyl (aryl-SO₂O-CH-CH₂OH).

[These groups can be converted into the α -amino- β -hydroxyethyl group by reaction with ammonia in the presence or absence of a solvent.]

D) α -carboxamido- β -hydroxyethyl (H₂NCO-CH-CH₂OH),

α -carbohydrazido- β -hydroxyethyl (H₂N-NH-CO-CH-CH₂OH),

α -carboxazido- β -hydroxyethyl (N₃CO-CH-CH₂OH) and

α -carbalkoxyhydroxamido- β -hydroxyethyl (alkyl-COONHCO-CH-CH₂OH).

[These groups can be converted into the α -amino- β -hydroxyethyl group by the Hofmann, Curtius, Schmidt or Lossen degradation or rearrangement respectively via the corresponding α -isocyanato- β -hydroxyethyl groups.]

E) α -Carboxy- α -amino- β -hydroxyethyl.

[This group is convertible into the α -amino- β -hydroxyethyl group by decarboxylation (e.g. by mild heating)].

The hydrogenation of a benzylidene-hydrazide of formula IIa or an acid addition salt thereof in accordance with one embodiment of the process of this invention is preferably effected catalytically; for example, by means of a platinum oxide or palladium-charcoal catalyst.

When a benzylidene-hydrazide of formula IIa or a compound of IIb whose configuration corresponds to that of *L*-serine is used as the starting material, correspondingly configured end-products are obtained directly. This embodiment of the process is preferred. When using a racemic starting material of formula IIa or IIb, the antipode derived from *L*-serine must be isolated from the racemate obtained. This can be effected in the usual manner by means of an optically active acid; for example, using tartaric acid or camphorsulphonic acid.

When the base is obtained as the product, this can be converted into an acid addition salt with an inorganic or an organic acid; for example, into the hydrochloride, the sulfate, the acetate or the oxalate. The acid addition salts are preferred over the base because of their greater stability.

A preferred embodiment of the process in accordance with the invention consists in catalytically hydrogenating an acid addition salt of N¹-*L*-serine-N²-(2,3,4-trihydroxy-benzylidene)-hydrazide, especially the hydrochloride, preferably using a palladium-charcoal catalyst. In doing this, the corresponding acid addition salt of N¹-*L*-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide is obtained directly.

The same product can also be obtained by catalytically hydrogenating an acid addition salt of N¹-*L*-serine-N²-(2,3,4-tribenzyloxy-benzylidene)-hydrazide, prefer-

②

ably using a palladium-charcoal catalyst. In this case, hydrogenolysis of the benzyloxy groups takes place first and subsequently hydrogenation of the benzylidene group occurs, an acid addition salt of N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide being obtained.

5 The benzylidene-hydrazides of formula IIa and the compounds of IIb as well as their acid addition salts used as starting materials in the process in accordance with the invention can be obtained according to known methods. The benzylidene-hydrazides of formula IIa are obtained by reacting an acid addition salt of racemic or L-serine hydrazide with 2,3,4-trihydroxybenzaldehyde. Compounds of formula 10 IIb can be obtained by reacting a correspondingly substituted serine hydrazide with a correspondingly substituted benzaldehyde and subsequently hydrogenating the benzylidene compound obtained (e.g. using a platinum catalyst).

15 The benzylidene-hydrazide of formula IIa which is derived from L-lysine, and its acid addition salts, are novel and it will be appreciated that they also form part of this invention. They are the novel benzylidene-hydrazide derivatives referred to hereinbefore. 15

The novel benzyl-hydrazide derivatives provided by the present invention (that is to say, the compound of formula I, which is derived from L-serine, and its acid addition salts) display pharmacological activity in that they possess a decarboxylase-inhibiting activity. 20

However, these novel benzyl-hydrazide derivatives are of particular interest in that, in combination with L-dopa, they represent outstanding agents for the treatment of Parkinsonism. Moreover, in combination with L-dopa they act antidepressively and the antidepressive activity of tricyclic amines, for example, of imipramine, is also potentiated by this combination. 25

It has been determined that in rats small doses (12 mg/kg) of N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride augment for at least 4 hours the enhancement of L-3,4-dihydroxy-phenylalanine (L-dopa) in the blood and in the brain induced by intraperitoneal or oral administration of this amino acid. At the same time, the increase of catecholamines (CA) and their metabolites, the phenol-carboxylic acids, is strongly reduced in the blood and other peripheral organs (heart, kidneys and spinal cord), but considerably augmented in the brain. As a consequence of the decrease of the catecholamine content in the periphery, the peripheral adrenergic stimulation is also diminished. On the other hand, the catecholamine depots in the extrapyramidal centres of the brain are extraordinarily strongly enhanced. 30 35

It is assumed that this effect is the consequence of a relatively selective inhibition of the decarboxylase by the N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride in the extracerebral organs. As a consequence of the enhanced dopa concentration in the blood, larger amount of amino acid get into the brain, where the decarboxylation to catecholamines takes place because the cerebral decarboxylase is practically uninhibited. This selective activity of N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide is indeed the consequence of a very low capability of this compound of penetrating into the brain. Thus, the decarboxylase activity in the brain of animals to which N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride has been injected is not markedly inhibited up to doses of 50 mg/kg, whilst in the heart and about 80% inhibition is observed at a dosage of 25 mg/kg. On the other hand, when it is added to homogenised tissue, the aforementioned hydrochloride causes the same decarboxylase inhibition both in the brain and in the heart. 40 45

To determine the activity on the enhancement of the catecholamine content in the brain induced by dopa, N¹-L-serine-N²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride was administered orally to the experimental animals (rats) in doses of 3—100 mg/kg. Thirty minutes later, 3 mg/kg of L-dopa were administered orally and the animals were killed 1 hour later. It was found that 12—24 mg/kg of the hydrazide hydrochloride induced the maximal enhancement of the catecholamines in the rat brain. This value is approximately 60 times higher than that which is obtained on the administration of L-dopa alone. 50 55

For the purpose of antiparkinson treatment, as well as for the purpose of treating depressive states, the combination of the novel benzyl-hydrazide derivatives provided by this invention with L-dopa can be administered both as an actual combination in a single dosage form or separately in two dosage forms. Since it has been found to be expedient that the L-dopa only be released in the body after the benzyl-hydrazide derivative, that is to say, preferably about 30—60 minutes after the benzyl-hydrazide derivative, in the case of administration of a single dosage form the L-dopa should be present in this in such a form that it is only released after the benzyl-hydrazide derivative. Such a combination with delayed dopa release 60 65

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can, for example, consist of a nucleus of *L*-dopa with a coating resistant to gastric juice. This nucleus can display an outer layer which contains the benzyl-hydrazide derivative, or the benzyl-hydrazide derivative, in the form of a granulate, can be incorporated in a capsule together with the *L*-dopa nucleus. In the case of parenteral application of the combination, the benzyl-hydrazide derivative is expediently first administered intramuscularly and, about 30—60 minutes later, the *L*-dopa is administered intravenously.

Of considerable significance is the quantitative ratio of benzyl-hydrazide derivative to *L*-dopa. This should amount to 0.5 to 2 parts by weight, preferably one part by weight, per part by weights of *L*-dopa. 225 mg to 600 mg of benzyl-hydrazide derivative and 450 mg to 600 mg of *L*-dopa (divided into 3—4 administrations) are expediently administered daily.

It will be appreciated that the invention also includes within its scope pharmaceutical preparations which contain the novel benzyl-hydrazide derivatives provided by the invention in association with a compatible pharmaceutical carrier.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

A) The preparation of the starting material:

15.4 g of 2,3,4-trihydroxybenzaldehyde are dissolved in 200 ml of boiling water, whereupon 15.2 g of *L*-serine-hydrazide hydrochloride are added to and dissolved in the resulting solution. The solution is concentrated under reduced pressure and the water is gradually displaced by the portionwise addition of ethanol. The resulting crystals are separated from the mother liquor by filtration and washed with ethanol and ether. *N*¹-*L*-Serine-*N*²-(2,3,4-trihydroxybenzylidene)-hydrazide hydrochloride of melting point 260°—265°C is obtained. $[\alpha]_D = +23^\circ$ (*c*=1; H₂O).

B) The process:

21 g of *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxy-benzylidene)-hydrazide hydrochloride are suspended in 300 ml of methanol and hydrogenated by means of a palladium-charcoal catalyst, dissolution being effected with the uptake of 1700 ml of hydrogen. After filtering off the catalyst, the filtrate is concentrated under reduced pressure, the resulting viscous residue is dissolved in a small quantity of ethanol and diluted with 600—700 ml of ethyl acetate, whereupon a powdery, amorphous precipitate is formed. This precipitate is filtered off, washed with ethyl acetate and ether and dried under reduced pressure over phosphorus pentoxide. The *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxy-benzyl)-hydrazide hydrochloride thus obtained is an amorphous powder, readily soluble in water, which decomposes at about 120°C with effervescence. $[\alpha]_D = -10^\circ$ (*c*=1; H₂O); $+18^\circ$ (*c*=1; dimethylformamide).

EXAMPLE 2

29 g of *N*¹-*L*-serine-*N*²-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate are suspended in 300 ml of methanol and hydrogenated using a palladium-on-carbon catalyst. After 4.6 litres of hydrogen have been taken up, 6.1 ml of benzyl chloride are added and the resulting mixture is further hydrogenated until hydrogen uptake ceases again, whereupon the catalyst is removed by filtration and the solution concentrated under reduced pressure. The product is then precipitated by dilution with ethyl acetate. It is identical with the product manufactured according to Example 1(B).

The aforementioned *N*¹-*L*-serine-*N*²-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate can be prepared as follows:

21.2 g of 2,3,4-tribenzyloxy-benzaldehyde are dissolved in 300 ml of boiling alcohol and treated with a solution of 7.2 g of *L*-serine-hydrazide hydrochloride and 7.1 ml of triethylamine in 30 ml of water. The mixture is boiled at reflux for 2—3 hours and allowed to cool. The resulting crystals are separated from the mother liquor by filtration and washed with alcohol and ether. The free base, *N*¹-*L*-serine-*N*²-(2,3,4-tribenzyloxy-benzylidene)-hydrazide obtained is then treated with acetic acid in known manner, to give the acetate. The *N*¹-*L*-serine-*N*²-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate thus obtained melts at 128°—130°C.

The following Examples illustrate pharmaceutical preparations containing the novel benzyl-hydrazide derivatives provided by the invention:

EXAMPLE A

A hard gelatin capsule in which the *L*-dopa component is present in delayed release form can be manufactured as follows:



A core consisting of 50 mg of *L*-dopa, 8 mg of corn starch, 15 mg of lactose, 1.8 mg of talc and 0.2 mg of magnesium stearate is coated with a cellulose acetate phthalate lacquer in order to make it resistant to gastric juice.

5 A granulate is manufactured in the usual manner from 50 mg of *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 58.25 mg of mannitol and 23.7 mg of polyvinylpyrrolidone.

The coated nucleus and the granulate are incorporated into a hard gelatin capsule.

EXAMPLE B

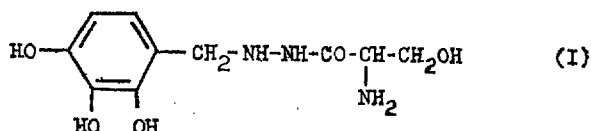
10 Tablets are manufactured in the usual manner, each tablet containing 150 mg of *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinylpyrrolidone, 1.5 mg of magnesium stearate and 13.5 mg of talc.

15 The aforementioned tablets are conveniently administered in combination with tablets containing 150 mg of *L*-dopa, 200 mg of lactose, 135 mg of corn starch, 1.5 mg of magnesium stearate and 13.5 mg of talc. These tablets can be manufactured in the usual manner.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 947,128.

20 WHAT WE CLAIM IS:—

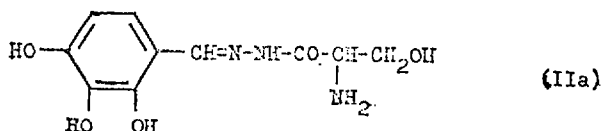
1. The compound of the formula



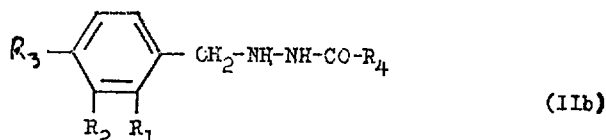
, which compound is derived from *L*-serine, and acid addition salts thereof.

25 2. *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride.

3. A process for the manufacture of the benzyl-hydrazide derivatives claimed in claim 1, which process comprises *either* hydrogenating a benzylidene-hydrazide of the formula



30 , which is present in the form of the racemate or of the antipode derived from *L*-serine, or an acid addition salt thereof, *or* converting in accordance with methods known *per se* the group or groups convertible into the hydroxy group and/or into the α -amino- β -hydroxyethyl group in a compound of the general formula



35 wherein *R*₁, *R*₂ and *R*₃ signify hydroxy groups or groups (as hereinafter defined) convertible into hydroxy groups and *R*₄ signifies the α -amino- β -hydroxyethyl group or a group (as hereinafter defined) convertible into the α -amino- β -hydroxyethyl group, at least one of the substituents *R*₁, *R*₂, *R*₃ and *R*₄ being different from the hydroxy group or from the α -amino- β -hydroxyethyl group,

40 which compound is present in the form of the racemate or of the antipode derived from *L*-serine, or in an acid addition salt of such a compound, into the hydroxy group or into the α -amino- β -hydroxyethyl group, *and* isolating the antipode derived from *L*-serine from a racemate obtained, and, if desired, converting a base obtained into an acid addition salt.

A core consisting of 50 mg of *L*-dopa, 8 mg of corn starch, 15 mg of lactose, 1.8 mg of talc and 0.2 mg of magnesium stearate is coated with a cellulose acetate phthalate lacquer in order to make it resistant to gastric juice.

5 A granulate is manufactured in the usual manner from 50 mg of *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 58.25 mg of mannitol and 23.7 mg of polyvinylpyrrolidone. 5

The coated nucleus and the granulate are incorporated into a hard gelatin capsule.

EXAMPLE B

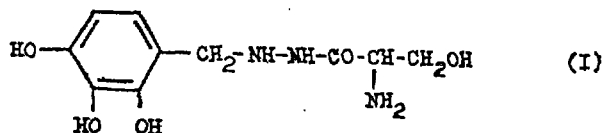
10 Tablets are manufactured in the usual manner, each tablet containing 150 mg of *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinylpyrrolidone, 1.5 mg of magnesium stearate and 13.5 mg of talc. 10

15 The aforementioned tablets are conveniently administered in combination with tablets containing 150 mg of *L*-dopa, 200 mg of lactose, 135 mg of corn starch, 1.5 mg of magnesium stearate and 13.5 mg of talc. These tablets can be manufactured in the usual manner. 15

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 947,128.

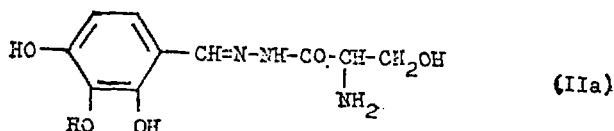
20 WHAT WE CLAIM IS:— 20

1. The compound of the formula

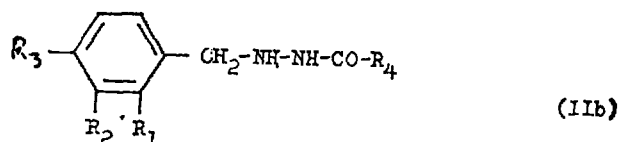


, which compound is derived from *L*-serine, and acid addition salts thereof.

25 2. *N*¹-*L*-serine-*N*²-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride. 25
3. A process for the manufacture of the benzyl-hydrazide derivatives claimed in claim 1, which process comprises *either* hydrogenating a benzylidene-hydrazide of the formula



30 , which is present in the form of the racemate or of the antipode derived from *L*-serine, or an acid addition salt thereof, *or* converting in accordance with methods known *per se* the group or groups convertible into the hydroxy group and/or into the α -amino- β -hydroxyethyl group in a compound of the general formula 30



35 wherein *R*₁, *R*₂ and *R*₃ signify hydroxy groups or groups (as hereinafter defined) convertible into hydroxy groups and *R*₄ signifies the α -amino- β -hydroxyethyl group or a group (as hereinafter defined) convertible into the α -amino- β -hydroxyethyl group, at least one of the substituents *R*₁, *R*₂, *R*₃ and *R*₄ being different from the hydroxy group or from the α -amino- β -hydroxyethyl group, 35
40 which compound is present in the form of the racemate or of the antipode derived from *L*-serine, or in an acid addition salt of such a compound, into the hydroxy group or into the α -amino- β -hydroxyethyl group, *and* isolating the antipode derived from *L*-serine from a racemate obtained, and, if desired, converting a base obtained into an acid addition salt. 40



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4. A process according to claim 3, wherein an acid addition salt of N¹-L-serine-N²-(2,3,4-trihydroxy-benzylidene)-hydrazide is catalytically hydrogenated.

5. A process according to claim 4, wherein said acid addition salt is the hydrochloride.

5 6. A process according to claim 4 or claim 5, wherein the catalytic hydrogenation is carried out using a palladium-on-carbon catalyst. 5

7. A process as claimed in claim 3 for the manufacture of the benzyl-hydrazide derivatives set forth in claim 1, substantially as hereinbefore described with reference to Examples 1 and 2.

10 8. Benzyl-hydrazide derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 3 to 7 inclusive. 10

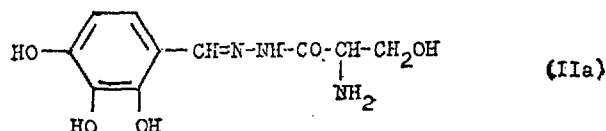
9. A pharmaceutical preparation comprising a benzyl-hydrazide derivative as claimed in claim 1 in association with a compatible pharmaceutical carrier.

15 10. A pharmaceutical preparation according to claim 9, wherein L-dopa or an acid addition salt thereof is also present. 15

11. A pharmaceutical preparation according to claim 10, wherein the quantitative ratio of the benzyl-hydrazide derivative to L-dopa is 0.52—2 parts by weight of benzyl-hydrazide derivative per part by weight of L-dopa.

12. The benzylidene-hydrazide of the formula

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, which is derived from L-serine, and acid addition salts thereof.

CARPMAELS & RANSFORD,
Agents for the Applicants.

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