

PATENT SPECIFICATION

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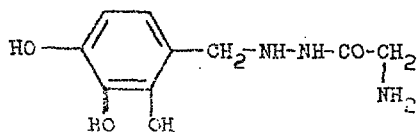
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(54) NOVEL BENZYL-HYDRAZIDE DERIVATIVES AND A
 PROCESS FOR THE MANUFACTURE THEREOF AND NOVEL
 BENZYLIDENE-HYDRAZIDE DERIVATIVES USEFUL IN SAID
 PROCESS

- (71) We, F. HOFFMAN-LA ROCHE & Co., AKTIENGESSELLSCHAFT, 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.

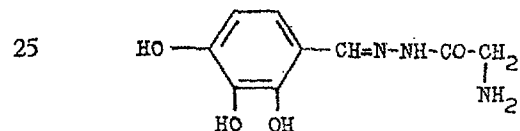
- The novel benzyl - hydrazide derivatives provided by the present invention are the compound of the formula



(I)

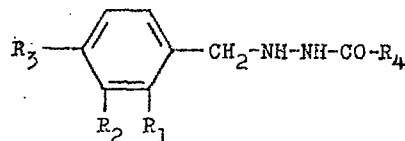
and acid addition salts thereof.

- According to the process provided by the invention, the novel benzyl - hydrazide derivatives aforesaid (that is to say, the compound of formula I and its acid addition salts) are manufacture either by hydrogenating the benzylidene - hydrazide of the formula



(IIa)

or an acid addition salt thereof, or by converting in accordance with methods known *per se* the groups or groups convertible into the hydroxy group and/or into the aminomethyl group in a compound of the general formula



(IIb)

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 aminomethyl group or a group (as hereinafter defined) convertible into the aminomethyl 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 aminomethyl group,

or in an acid addition salt of such a compound, into the hydroxy group or into the aminomethyl group, 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 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

- 5 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 the hydroxy group by hydrolysis. 10 15
- The groups convertible into the aminomethyl group [$-\text{CH}_2-\text{NH}_2$] designated by R_4 in formula IIb are classified as follows:

- 20 A) carbobenzoxyaminomethyl (benzyl-OCO-NH-CH₂-),
benzylaminomethyl (benzyl-NH-CH₂-),
benzhydrylaminomethyl [(C₆H₅)₂-CH-NH-CH₂-],
benzylideneaminomethyl (phenyl-CH=N-CH₂-),
azidomethyl (N₃-CH₂-), cyano (-CN), nitromethyl (O₂N-CH₂-),
25 phenylazomethyl (phenyl-N=N-CH₂-),
hydroximinomethyl (HON=CH-), iminomethyl (HN=CH-) and
phenylhydrazonomethyl (phenyl-NH-N=CH-).

[These groups can be converted into the aminomethyl group in accordance with methods known *per se*; for example, by 30 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 aminomethyl group by means of chemical reducing agents (e.g. metal hydrides)]. 35

- 40 B) formylaminomethyl (OHC-NH-CH₂-),
trifluoroacetylaminomethyl (F₃C-CONH-CH₂-),
tritylaminomethyl [(C₆H₅)₃C-NH-CH₂-],
o - nitrophenylsulfenylaminomethyl (*o* - nitrophenyl-S-NH-CH₂-),
alkoxycarbonylaminomethyl (alkyl-O-CONH-CH₂-) and
phthalimidomethyl.

[These groups can be converted into the aminomethyl group by hydrolysis in accordance with methods known *per se*. Thus, the 45 hydrolysis of the formylaminomethyl group can be effected by means of dilute alcoholic hydrochloric acid, whereas the hydrolysis of the trifluoroacetylaminomethyl group may also be effected by means of a dilute aqueous ammonia solution. The phthalimidomethyl group is suitable converted into the aminomethyl group by means of hydrazine]. 50

- 55 C) halomethyl (hal-CH₂-),
alkylsulfonyloxymethyl (alkyl-SO₂-O-CH₂-) and
arylsulfonyloxymethyl (aryl-SO₂-O-CH₂-).

[These groups can be converted into the aminomethyl group by reaction with ammonia in the presence or absence of a solvent].

- 60 D) carboxamidomethyl (H₂N-CO-CH₂-),
carbohydrazidomethyl (H₂N-NH-CO-CH₂-),
carboxazidomethyl (N₃OC-CH₂-) and
carbalkoxyhydroamidomethyl (alkyl-COONH-CO-CH₂-).

[These groups can be converted into the aminomethyl group by means of the 65 HOFMANN, CURTIUS, SCHMIDT or LOSSEN degradation or rearrangement, respectively]. 75

- E) α -Carboxy- α -aminomethyl.

[This group can be converted into the aminomethyl group by decarboxylation (e.g. by mild heating)]. 70

The hydrogenation of the 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-on-carbon catalyst. The latter is particularly preferred. 75

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. Because of their 80

greater stability, the acid addition salts are preferred over the base.

5 A preferred embodiment of the process in accordance with the invention consists in catalytically hydrogenating and acid addition salt, especially the hydrochloride, of N¹ - glycine - N² - (2,3,4 - trihydroxybenzylidene) - hydrazide, preferably using a
10 palladium-on-carbon catalyst. In this case, the corresponding salt of N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide is obtained directly.

15 The same product can also be obtained by catalytically hydrogenating an acid addition salt of N¹ - glycine - N² - (2,3,4 - tribenzyloxybenzylidene) - hydrazide, preferably using a palladium - charcoal catalyst. In this case there first occurs hydrogenolysis of the benzyloxy groups and thereafter hydro-
20 genation of the benzylidene group, a salt of N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide being obtained.

25 The benzylidene - hydrazide of formula IIa and the compounds of formula 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.

30 The benzylidene - hydrazide of formula IIa is obtained by reacting an acid addition salt of glycine hydrazide with 2,3,4 - trihydroxy - benzaldehyde. Compounds of formula IIb can be obtained by reacting a correspondingly substituted glycine hydrazide with a correspondingly substituted benzaldehyde and subsequently hydrogenating the benzylidene compound obtained (e.g. using a platinum catalyst).

40 The benzylidene - hydrazide of formula IIa and its acid addition salts are the novel benzylidene - hydrazide derivatives referred to earlier and it will be appreciated that they also form part of this invention.

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

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

60 It has been determined that in rats small doses (12 mg/kg) of N¹ - glycine - 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
65 brain induced by intraperitoneal or oral ad-

ministration of this amino acid. At the same time, the increase of catecholamines (CA) and their metabolites, the phenol carboxylic acids, in the blood and other peripheral organ (heart, kidneys and spinal cord) is strongly reduced, 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.

70 It is assumed that this effect is the consequence of a relatively selective inhibition of the decarboxylase by the N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride in the extracerebral organs. As a consequence of the enhanced dopa concentration in the blood, larger amounts 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 - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide is indeed the consequence of a very low
80 capability of this compound of penetrating into the brain. Thus, the decarboxylase activity in the brain of animals to which N¹ - glycine - 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 an about 80% inhibition is already 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.

100 To determine the activity on the enhancement of the catecholamine content in the brain induced by dopa, N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride was administered orally to 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.

105 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 and 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
110 115 120 125 130

derivative, in the case of administration of a single dosage form the *L* - dopa should be present therein in such a form that it is only released after the benzyl - hydrazide derivative. Such a combination with delayed dopa release 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 coated *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 1 part by weight) per part by weight of *L* - dopa. 225 mg to 600 mg of benzyl - hydrazide derivative and 450 mg to 600 mg of *L* - dopa (divided into 3 to 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 medicinally acceptable 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 and treated with 12.6 g of glycine hydrazide monohydrochloride. After a few minutes, the liquid becomes turbid and soon solidifies forming a crystalline mass. This mass is cooled in ice-water, filtered, and washed with a small quantity of water and with a large amount of acetone. The N^1 - glycine - N^2 - (2,3,4 - trihydroxy - benzylidene) - hydrazide hydrochloride thus obtained forms white to yellowish crystals and melts at 303°—305°C with decomposition.

B) The process:

24 g of N^1 - glycine - N^2 - (2,3,4 - trihydroxy - benzylidene) - hydrazide hydrochloride are suspended in 300 ml of water and hydrogenated with palladium-on-carbon. With fairly rapid uptake of 2.5 litres of hydrogen, there is obtained a clear solution. The catalyst is removed by filtration and the filtrate is concentrated to a volume of 40—50 ml under reduced pressure and diluted with 200 ml of absolute ethanol. Crystallization takes place within a few seconds. The crystalline material is allowed to stand overnight in a refrigerator,

filtered and rinsed with ethanol, ether and petroleum ether. For further purification, the crude product is dissolved in 40 ml of water at a temperature not higher than 40°—50°C and crystallization is initiated by the addition of 120 ml of methanol. The N^1 - glycine - N^2 - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride thus obtained forms white crystals which are soluble in water with a neutral reaction. M.p. 179°—182°C.

EXAMPLE 2

31.5 g of N^1 - carbobenzoxyglycine - N^2 - (2,3,4 - tribenzylidene) - hydrazide are suspended in 300 ml of methanol and 5 ml of glacial acetic acid and hydrogenated with palladium-on-carbon. After the uptake of the calculated amount of hydrogen, 6.1 ml of benzyl chloride are added and the mixture is further hydrogenated until the hydrogen uptake ceases. The catalyst is removed by filtration and the filtrate is evaporated under reduced pressure to give a crystalline mass. The product obtained is identical with the product obtained in accordance with Example 1(B).

The aforementioned N^1 - carbobenzoxyglycine - N^2 - (2,3,4 - tribenzylidene) - hydrazide can be prepared as follows:

22.3 g of carbobenzoxy - glycine hydrazide and 42.4 g of 2,3,4 - tribenzylidenebenzaldehyde are each dissolved in 300 ml of boiling absolute ethanol. The two solutions are then combined with each other and boiled for an hour. After cooling in ice-water, the resulting solid product is separated by filtration and washed with alcohol and ether. The N^1 - carbobenzoxyglycine - N^2 - (2,3,4 - tribenzylidene) - hydrazide thus obtained melts at 140°—142°C.

EXAMPLE 3

By hydrogenating N^1 - carbobenzoxyglycine - N^2 - (2,3,4 - trihydroxy - benzylidene) hydrazide using a palladium-on-carbon catalyst in a mixture of methanol, water and glacial acetic acid, adding the calculated amount of benzyl chloride, further hydrogenating and working up in analogy to Example 2, a product identical with the product of Example 2 is obtained.

The aforementioned N^1 - carbobenzoxyglycine - N^2 - (2,3,4 - trihydroxybenzylidene) - hydrazide can be prepared as follows:

22.3 g of carbobenzoxy - glycine hydrazide are dissolved in 300 ml of boiling absolute ethanol and treated with 15.4 g of 2,3,4 - trihydroxybenzaldehyde. After boiling for a short time, the mixture is cooled in ice-water and filtered. The N^1 - carbobenzoxy - glycine - N^2 - (2,3,4 - trihydroxy - benzylidene) - hydrazide thus obtained melts at 211°—212°C.

EXAMPLE 4

N^1 - Nitroacetyl - N^2 - (2,3,4 - tribenzyl-

oxy - benzylidene) - hydrazide is dissolved in 200 ml of methanol and hydrogenated in the presence of a palladium catalyst in analogy to Example 2, N¹ - glycine - N² - (2,3,4 - trihydroxy - benzyl) - hydrazide being obtained via N¹ - glycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide. The hydrochloride of the product is identical with the product of Example 1(B).

The aforementioned N¹ - nitroacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide can be prepared as follows:

28 g of N¹ - bromoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide are treated with stirring at room temperature with 7.7 g of silver nitrite which are added in portions. The mixture is further stirred overnight, whereupon the silver bromide precipitate is removed by filtration. The filtrate is concentrated under reduced pressure to a volume of about 50 ml, diluted with chloroform, washed 4 to 5 times with water, dried over sodium sulfate and evaporated under reduced pressure. The N¹ - nitroacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide thus obtained forms a yellow, viscous oil.

The N¹ - bromoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide can, in turn, be obtained as follows:

11 g of 2,3,4 - tribenzyloxybenzaldehyde are dissolved in 200 ml of boiling absolute ethanol and the resulting solution is treated with a freshly prepared mixture of 6.5 g of bromoacetyl - hydrazide hydrochloride (melting point 180°—181°C), 3.9 ml of triethyl amine and 15 ml of water. (The bromoacetyl - hydrazide hydrochloride is obtained by reacting of bromo - acetic acid and N - hydroxy - succinimide in the presence of N,N' - dicyclohexylcarbodiimide, reacting the resulting 1 - bromoacetoxy - 3,5 - dioxopyrrolidine with carbobenzoxy - hydrazine in ethyl acetate at 0°—5°C and treating the resulting N¹ - bromoacetyl - N² - carbobenzoxy - hydrazide with acetic anhydride and hydrogen bromide). The reaction of the 2,3,4 - tribenzyloxybenzaldehyde and the bromoacetyl - hydrazide hydrochloride is soon completed and the mixture solidifies within 2—3 minutes to form a crystalline mass. The mixture is allowed to cool and is then filtered and washed with ethanol and ether. The N¹ - bromoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide thus obtained forms white crystals melting at 175°—176°C.

EXAMPLE 5

N¹ - Azidoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide is hydrogenated in analogy to Example 2, N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide being obtained via N¹ - glycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide.

The hydrochloride of the product is identical with the product of Example 1(B).

The aforementioned N¹ - azidoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide can be prepared as follows:

28 g of N¹ - bromoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide are added to 200 ml of dimethylformamide and the resulting mixture is treated with 3.3 g sodium azide, the latter being added in portions with stirring. The N¹ - azidoacetyl - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide is obtained in the form of an oil.

EXAMPLE 6

15 g of N¹ - tritylglycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide are suspended in 400 ml of methanol and hydrogenated in the presence of a palladium-on-carbon catalyst. Upon consumption of 1 mole of hydrogen, the catalyst is removed by filtration and the filtrate is treated with acetic anhydride, heated for 10—15 minutes on a steam bath and cooled in ice-water. The triphenyl carbinol precipitate formed is removed by filtration and the pH of the filtrate is adjusted to 2—3 by adding ethanolic hydrogen chloride. The mixture is then evaporated under reduced pressure to a volume of 100 ml. Upon removal of the triphenyl carbinol by filtration, the filtrate is evaporated until crystallization of the product. This product is identical with the product of Example 1(B).

The foregoing N¹ - tritylglycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide can be prepared as follows:

A mixture of 6.6 g of trityl - glycine - hydrazide (J.A.C.S. 78, 1359) and 3.1 g of 2,3,4 - trihydroxy - benzaldehyde is boiled in ethanol for 2—3 hours. Upon cooling and stirring the mixture in a refrigerator overnight, N¹ - tritylglycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide is obtained in crystalline form melting at 148°—150°C.

EXAMPLE 7

N¹ - Formylglycine - N² - (2,3,4 - trihydroxy - benzylidene) - hydrazide [obtained by reacting 5.1 g of formyl - glycine - hydrazide (J. Chem. Soc. 1954, 1039) with 6.3 g of 2,3,4 - trihydroxy - benzaldehyde] is suspended in 200 ml of methanol and hydrogenated in the presence of a palladium-on-carbon catalyst. Upon consumption of 1 mole of hydrogen, the catalyst is removed by filtration and the pH of the filtrate is adjusted to 1—2 by adding methanolic hydrochloric acid. The solution is then allowed to stand at room temperature for 2—3 days, during which time the formyl group is split off. The solution is then concentrated under reduced pressure until crystallization. The product is identical with the product of Example 1(B).

EXAMPLE 8

A mixture of 10.6 g of trifluoroacetyl - glycine - hydrazide [Chem. Ber. 92 (1959) 313] and 6.3 g of 2,3,4 - trihydroxy - benzaldehyde is suspended in 200 ml of methanol, 7.1 ml of triethylamine are added and the mixture is hydrogenated in the presence of a palladium-on-carbon catalyst. Upon consumption of 1 mole of hydrogen, the catalyst is separated by filtration and the filtrate is treated with 10 ml of a 2N methanolic ammonia solution and allowed the stand for 24 hours under a nitrogen atmosphere at room temperature, during which time the trifluoroacetyl group is split off. The pH of the mixture is adjusted to 2.5—3 by adding ethanolic hydrochloric acid and the solution is concentrated under reduced pressure to a volume of 100 ml. The ammonium chloride precipitate is removed by filtration and the filtrate is concentrated until crystallization sets in (i.e. to a volume of about 60 ml). The product thus obtained is identical with the product of Example 1(B).

EXAMPLE 9

A mixture of 6.25 g of glycine - hydrazide and 41.4 g of 2,3,4 - tribenzyloxy - benzaldehyde is boiled in 500 ml of ethanol for 3—4 hours. The viscous mass which separates on cooling solidifies in 2—3 days. The solid substance is separated by filtration and washed with ethanol and ether. The N¹ - (2,3,4 - tribenzyloxy - benzylidene - glycine) - N² - (2,3,4 - tribenzyloxy - benzylidene) - hydrazide thus obtained melts at 110°—115° C with decomposition.

10 g of the hydrazide thus obtained are suspended in 300 ml of methanol and hydrogenated in the presence of a palladium-on-carbon catalyst until complete termination of hydrogen consumption. The catalyst is removed by filtration, the filtrate is acidified (to a pH of 2.5—3) by adding ethanolic hydrochloric acid and the mixture is concentrated under reduced pressure until crystallization. The product thus obtained is identical with the product of Example 1(B).

EXAMPLE 10

11 g of phthalyl - glycine - hydrazide (C.A. 52, 14540^a) are suspended in 300 ml of boiling ethanol, whereupon 6.7 g of 2,3,4 - trihydroxy - benzaldehyde are added. By boiling the mixture for 2 hours, there is obtained a clear solution. This solution is hydrogenated in the presence of a palladium-on-carbon catalyst until complete termination of hydrogen consumption. The catalyst is then removed by filtration and 1.5 ml of hydrazine hydrate are added to the filtrate. The phthalylhydrazide which precipitates on standing overnight is removed by filtration and the filtrate is acidified (to a pH of 2.5—3) by adding ethanolic hydrochloric acid. The solu-

tion is concentrated under reduced pressure to a volume of 100 ml and the hydrazine hydrochloride precipitate formed is removed by filtration. The filtrate is further concentrated to 60 ml, whereupon the product precipitates. This product is identical with the product of Example 1(B).

EXAMPLE 11

8.9 g of benzyl - glycine - hydrazide (Arch. Pharm. 295, 697) are boiled at reflux together with 6.7 g of 2,3,4 - trihydroxy - benzaldehyde in 300 ml of methanol for 3—4 hours, whereupon the mixture is hydrogenated in the presence of a palladium-on-carbon catalyst. Upon completion of hydrogen consumption, the catalyst is removed by filtration, the filtrate is acidified (pH 2.5—3) by adding ethanolic hydrochloric acid and the mixture is concentrated under reduced pressure until crystallization sets in. The product thus obtained is identical with the product of Example 1(B).

EXAMPLE 12

17.8 g of carbobenzoxyamino - malonic acid benzyl ester - hydrazide (obtained by the reaction of hydrazine hydrate with carbobenzoxyamino - malonic acid benzyl ester - methyl ester) and 21.3 g of tribenzyloxy - benzaldehyde are boiled in 1 liter of methanol for 3—4 hours. The mixture is allowed to cool to room temperature and hydrogenated in the presence of a palladium-on-carbon catalyst until completion of hydrogen consumption. The catalyst is removed by filtration, the filtrate is acidified (to pH 2.5—3) by adding ethanolic hydrochloric acid and the mixture is concentrated under reduced pressure until crystallization sets in. The product thus obtained is identical with the product of Example 1(B).

EXAMPLE 13

6 g of malonic acid - semihydrazide (B. 54, 1432) are dissolved in 200 ml of ethanol, whereupon 6.7 g of 2,3,4 - tribenzyloxy - benzaldehyde are added. The mixture is heated at reflux for 30 minutes and then hydrogenated in the presence of a palladium-on-carbon catalyst. The filtrate obtained upon completion of hydrogen consumption and removal of the catalyst by filtration is evaporated under reduced pressure. The residue is a brown oil which is dissolved in 60 ml of concentrated sulfuric acid with cooling. 3.3 g of sodium azide are then added with ice-cooling, the mixture is allowed to stand overnight and is then diluted with ice water to a volume of 500 ml. The sulfate ions are removed by the addition of barium chloride and separation of the resulting barium sulfate precipitate. The filtrate is concentrated under reduced pressure and the water is removed by repeated addition of methanol and evapora-

tion. The solution is then diluted with ethanol to a volume of 400 ml and the sodium chloride precipitate is removed by filtration. The filtrate is brought to a pH of 2.5—3, purified with carbon and concentrated under reduced pressure until crystallization sets in. The product thus obtained is identical with the product of Example 1(B).

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

EXAMPLE A

A hard gelatin capsule from which the *L* - dopa component is released with delay can be manufactured as follows:

A nucleus 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.

A granulate is manufactured in the usual manner from 50 mg of N^1 - glycine - 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

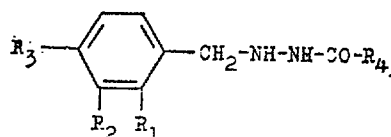
Tablets are manufactured in the usual manner, each tablet containing 150 mg of N^1 - glycine - N^2 - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinylpyrrolidone, 155 mg of magnesium stearate and 13.5 mg of talc.

These tablets are administered about 30—60 minutes before tablets which contain 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 and which are 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.

WHAT WE CLAIM IS:—

1) The compound of the formula

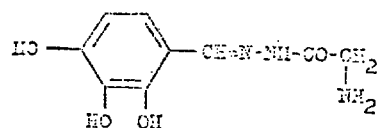


(I)

and acid addition salts thereof.

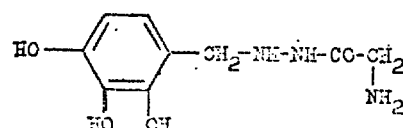
2) N^1 - Glycine - N^2 - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride.

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



(IIa)

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 aminomethyl group in a compound of the general formula



(IIb)

wherein R_1 , R_2 and R_3 signify hydroxy groups or groups (as hereinbefore defined) convertible into hydroxy groups and R_4 signifies the aminomethyl group or a group (as hereinbefore defined) convertible into the aminomethyl 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 aminomethyl group,

or in an acid addition salt of such a compound, into the hydroxy group or into the aminomethyl group, and, if desired, converting a base obtained into an acid addition salt.

4) A process according to claim 3, wherein an acid addition salt of N^1 - glycine - N^2 - (2,3,4 - trihydroxy - benzylidene) - hydrazide is catalytically hydrogenated.

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

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

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 to 13.

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



tion. The solution is then diluted with ethanol to a volume of 400 ml and the sodium chloride precipitate is removed by filtration. The filtrate is brought to a pH of 2.5—3, purified with carbon and concentrated under reduced pressure until crystallization sets in. The product thus obtained is identical with the product of Example 1(B).

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

EXAMPLE A

A hard gelatin capsule from which the L - dopa component is released with delay can be manufactured as follows:

A nucleus 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.

A granulate is manufactured in the usual manner from 50 mg of N¹ - glycine - N² - (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

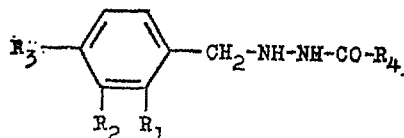
Tablets are manufactured in the usual manner, each tablet containing 150 mg of N¹ - glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinylpyrrolidone, 155 mg of magnesium stearate and 13.5 mg of talc.

These tablets are administered about 30—60 minutes before tablets which contain 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 and which are 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.

WHAT WE CLAIM IS:—

1) The compound of the formula

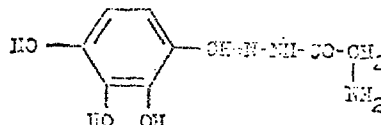


(I)

and acid addition salts thereof.

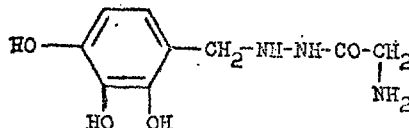
2) N¹ - Glycine - N² - (2,3,4 - trihydroxybenzyl) - hydrazide hydrochloride.

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



(IIa)

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 aminomethyl group in a compound of the general formula



(IIb)

wherein R₁, R₂ and R₃ signify hydroxy groups or groups (as hereinbefore defined) convertible into hydroxy groups and R₄ signifies the aminomethyl group or a group (as hereinbefore defined) convertible into the aminomethyl group, at least one of the substituents R₁, R₂, R₃ and R₄ being different from the hydroxy group or from the aminomethyl group,

or in an acid addition salt of such a compound, into the hydroxy group or into the aminomethyl group, and, if desired, converting a base obtained into an acid addition salt.

4) A process according to claim 3, wherein an acid addition salt of N¹ - glycine - 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.

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

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 to 13.

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

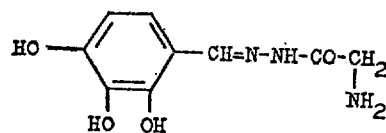


9) A pharmaceutical preparation comprising a benzyl - hydrazide derivative as set forth in claim 1 in association with a compatible medicinally acceptable carrier.

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

10 11) A pharmaceutical preparation according to claim 10, wherein the quantitative ratio of the benzyl - hydrazide derivative to *L* - dopa is 0.5—2 parts by weight of benzyl - hydrazide derivative to one part by weight of *L* - dopa.

15 12) The benzylidene - hydrazide of the formula



(IIa)

and acid addition salts thereof.

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