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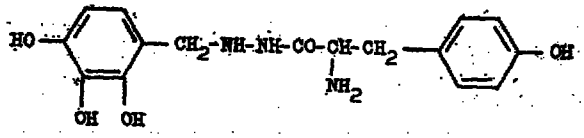
(54) NOVEL BENZYL-HYDRAZIDE DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF AND NOVEL BENZYLIDENE-HYDRAZIDE DERIVATIVES USEFUL IN SAID PROCESS

(71) We, F. HOFMANN-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.

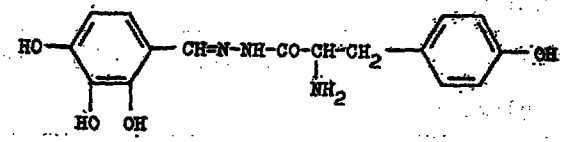
The novel benzyl-hydrazide derivatives provided by this invention are the compound of the formula



(I)

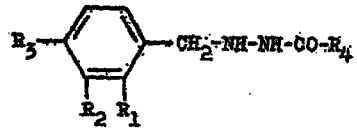
and acid addition salts thereof.

According to the process provided by the invention, the novel benzyl-hydrazide derivatives aforesaid are manufactured *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 group or groups convertible into the hydroxy group and/or into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group in a compound of the general formula



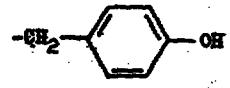
(IIb)

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 α-amino-β-(*p*-hydroxyphenyl)-ethyl group or a group (as hereinafter defined) convertible into the α-amino-β-(*p*-hydroxyphenyl)-ethyl 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-(*p*-hydroxyphenyl)-ethyl group, or in an acid addition salt of such a compound, into the hydroxy group and/or into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group *and*, if desired, splitting a racemate obtained into the optical antipodes and, also 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 tetrahydropyran (e.g. α-ethoxy-ethoxy, α-methoxy-*iso*propoxy 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. with noble-metal catalysts such as palladium and platinum catalysts) and the acyloxy groups can be converted into the hydroxy group by hydrolysis.

The groups convertible into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group are classified as follows, the symbol R_5 in the following formulae representing the group



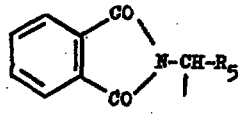
A)

α-carbobenzoxyamino-β- -(*p*-hydroxyphenyl)-ethyl	$C_6H_5—CH_2—OCONH—\underset{\displaystyle R_5}{\underset{\vert}{CH}}—$
α-benzylamino-β- -(*p*-hydroxyphenyl)-ethyl	$C_6H_5—CH_2—NH—\underset{\displaystyle R_5}{\underset{\vert}{CH}}—$
α-benzylideneamino-β- -(*p*-hydroxyphenyl)-ethyl	$C_6H_5—CH=N—\underset{\displaystyle R_5}{\underset{\vert}{CH}}—$
α-benzhydrylamino-β- -(*p*-hydroxyphenyl)-ethyl	$(C_6H_5)_2—CH_2—NH—\underset{\displaystyle R_5}{\underset{\vert}{CH}}—$

α-azido-β- -(*p*-hydroxyphenyl)-ethyl	$N_3—CH(—R_5)$
α-nitro-β- -(*p*-hydroxyphenyl)-ethyl	$O_2N—CH(—R_5)$
α-phenylazo-β- -(*p*-hydroxyphenyl)-ethyl	$C_6H_5—N=N—CH(—R_5)$
α-hydroximino-β- -(*p*-hydroxyphenyl)-ethyl	$HO—N=C(—R_5)$
α-phenylhydrazono-β- -(*p*-hydroxyphenyl)-ethyl	$C_6H_5—NH—N=C(—R_5)$

[These groups can be converted into the α-amino-β-(*p*-hydroxyphenyl)-ethyl 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-(*p*-hydroxyphenyl)-ethyl group by means of chemical reducing agents (e.g. metal hydrides).

B)

α-formylamino-β- -(*p*-hydroxyphenyl)-ethyl	$OHC—NH—CH(—R_5)$
α-trifluoroacetylamino-β- -(*p*-hydroxyphenyl)-ethyl	$F_3C—CONH—CH(—R_5)$
α-tritylamino-β- -(*p*-hydroxyphenyl)-ethyl	$(C_6H_5)_3—C—NH—CH(—R_5)$
α-alkoxycarbonylamino-β- -(*p*-hydroxyphenyl)-ethyl	$alkyl—O—CONH—CH(—R_5)$
α-phthalimido-β- -(*p*-hydroxyphenyl)-ethyl	

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

c) α-halo-β-(*p*-hydroxyphenyl)-ethyl groups such as α-bromo-β-(*p*-hydroxyphenyl)-ethyl ($Br—\underset{|}{CH}—R_5$), α-alkylsulfonyloxy-β-(*p*-hydroxyphenyl)-ethyl groups

$$(alkyl\text{-}SO_2—O—\underset{|}{CH}—R_5)$$

and α-arylsulfonyloxy-β-(*p*-hydroxyphenyl)-ethyl groups ($aryl\text{-}SO_2—O—\underset{|}{CH}—R_5$).

[These groups can be converted into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group by reaction of ammonia in the presence or absence of a solvent.]

D)

α-carboxamido-β- -(*p*-hydroxyphenyl)-ethyl	$H_2NCO—\underset{|}{CH}—R_5$
α-carbohydrazido-β- -(*p*-hydroxyphenyl)-ethyl	$H_2N—NHCO—\underset{|}{CH}—R_5$
α-carboxazido-β- -(*p*-hydroxyphenyl)-ethyl	$N_3—CO—\underset{|}{CH}—R_5$
α-carbalkoxyhydroxamido-β- -(*p*-hydroxyphenyl)-ethyl	$alkyl—COONHCO—\underset{|}{CH}—R_5$

[These groups can be converted into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group by the HOFMANN, CURTIUS, SCHMIDT or LOSSEN degradation or rearrangement, respectively, via the corresponding α-isocyanato-β-(*p*-hydroxyphenyl)-ethyl group.]

E) α-carboxy-α-amino-β-(*p*-hydroxyphenyl)-ethyl ($H_2N—\underset{\underset{COOH}{|}}{\overset{|}{C}}—R_5$)

[This group can be converted into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group by decarboxylation (e.g. by mild heating)].

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

Where a benzylidene-hydrazide of formula IIa or a compound of formula IIb whose configuration corresponds to that of *L*-tyrosine 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 racemate obtained can be resolved into the optical antipodes. This can be effected in the usual manner by means of an optically active acid, for example with tartaric acid or camphorsulphonic acid. In this case, the antipode corresponding to *L*-tyrosine is preferably isolated.

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

A preferred embodiment of the process in accordance with the invention consists in catalytically hydrogenating an acid addition salt, especially the hydrochloride, of N^1-tyrosine-N^2-(2,3,4-trihydroxy-benzylidene)-hydrazide, preferably using a palladium-

on-carbon catalyst. In this case, the corresponding salt of N^1-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide is obtained directly.

The same product can also be obtained by catalytically hydrogenating an acid addition salt of N^1-tyrosine-N^2-(2,3,4-tribenzyloxy-benzylidene)-hydrazide, preferably using a palladium-on-carbon catalyst. In this case, there first occurs hydrogenolysis of the benzyloxy groups and thereafter hydrogenation of the benzylidene group, a salt of N^1-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide likewise being obtained.

In both cases, the antipodes derived from *L*-tyrosine are preferably used as the starting materials.

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

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.

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.

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 *L*-dopa, they act antidepressively and the antidepressive activity of tricyclic antidepressives, for example, of imipramine, is also potentiated by this combination.

It has been determined that in rats small doses (12 mg/kg) of N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride augment for at least 4 hours the enhancement of *L*-3,4-dihydroxy-phenylalamine (*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 metabilites, the phenol carboxylic acids, in the blood and other peripheral organs (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.

It is assumed that this effect is the consequence of a relatively selective inhibition of the decarboxylase by N^1-*L*-tyrosine-N^2-(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 N^1-*L*-tyrosine-N^2-(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 N^1-*L*-tyrosine-N^2-(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.

To determine the activity on the enhancement of the catecholamine content in the brain induced by dopa, N^1-*L*-tyrosine-N^2-(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 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.

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 derivative, in the case of the 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 juices. This nucleus can be surrounded by an outer layer which contains the benzyl-hydrazide derivative, or the benzyl-hydrazide derivative, in the form of a granulate, can be incorporated into 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, of the benzyl hydrazide 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, and that *L*-dopa or an acid addition salt thereof may also be present in said preparations.

The following Examples illustrate the process provided by the invention.

EXAMPLE 1

A) The preparation of the starting material:

8.1 g of *L*-tyrosine-hydrazide are heated in 500 ml of water to 80°—90° C., whereupon 9.5 ml of concentrated hydrochloric acid are added. The pH of the resulting colourless, clear solution is 3.4 to 3.6. A boiling solution of 13.4 g of 2,3,4-trihydroxy-benzaldehyde in 100 ml of water is then added and heating on a steam-bath is continued for 5—10 minutes. The solution is filtered in order to remove impurities and then concentrated under reduced pressure to a volume of about 250 ml. On cooling with ice there is obtained a crystalline mass which is separated by filtration and washed with a small quantity of ice-water. The product melts at 190°—195° C. with decomposition. $[\alpha]_D = +131°$ (c=1 in water). U.V. spectrum; $\lambda = 226$ mμ; 314 mμ; log $\varepsilon = 4.344$; 4.384.

B) The process:

73 g of N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxy-benzylidene)-hydrazide hydrochloride are suspended in 300 ml of water and hydrogenated in the presence of a 5% palladium-on-carbon catalyst. Hydrogenation is completed upon consumption of 5.4 liters of hydrogen. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure, the water being slowly replaced first by methanol and then by ethanol. The remaining solution (250—300 ml) is diluted with ethanol to a volume of 600 ml, whereupon the solution is allowed to stand for 2 to 3 days at minus 15° C. in order to effect crystallization. The crystals are separated and washed with ethanol, ether and petroleum ether. The N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxy-benzyl)-hydrazide hydrochloride thus obtained forms white crystals which are readily soluble in water with a neutral reaction and which melt at 229°—230° C. with decomposition. $[\alpha]_D = 0°$ (c=1 in water); $[\alpha]_D = +10°$ (c=1 in 1-*N*-hydrochloric acid); U.V. spectrum: $\lambda = 276$ mμ; log $\varepsilon = 3.399$ (in ethanol).

EXAMPLE 2

By hydrogenation of N^1-*L*-tyrosine-N^2-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate in the presence of palladium-on-carbon in a manner analogous to that described in Example 1(B) and conversion of the acetate obtained into the hydrochloride there is obtained a product identical with the product of Example 1(B).

The N^1-*L*-tyrosine-N^2-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate aforesaid can be obtained as follows:

A mixture of 9.2 g of *L*-tyrosine hydrazide, 200 ml of alcohol and 4 ml of glacial acetic acid is heated to boiling and treated with a boiling solution of 2,3,4-tribenzyloxy-benzaldehyde in 200 ml of ethanol. The mixture is boiled at reflux for 2—3 hours, allowed to stand overnight and, after filtering off a small amount of undissolved material, evaporated under reduced pressure to a syrupy consistency. The hydrazone acetate is precipitated with ether, a non-crystallizing, viscous mass being

formed. The crystals obtained after trituration of this mass was *iso*propanol and crystalization are washed with *iso*propanol and ether. N^1-*L*-tyrosine-N^2-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate with a melting point of 143°—145° C. is obtained.

EXAMPLE 3

A mixture of 13.4 g of *L*-N-carbobenzoxy-O-benzyl-tyrosine and 15.9 g of 2,3,4-tribenzyloxy-benzyl-hydrazine hydrochloride is added to 300 ml of methylene chloride, stirred and treated with 4.6 ml of triethylamine. 6.7 g of N,N'-di*cyclo*hexyl-carbodiimide are added and stirring is continued for 1 hour. The di*cyclo*hexylurea precipitate is removed by filtration and the methylene chloride solution is washed 2—3 times with water, dried over sodium sulfate and concentrated under reduced pressure. Crystallization occurs on dilution with ether. The *L*-N-carbobenzoxy-O-benzyl-tyrosine-(2,3,4-tribenzyloxy)-benzyl-hydrazide thus obtained melts at 153°—154° C.

9.8 g of the hydrazide obtained according to the preceding paragraph are suspended in 200 ml of methanol and hydrogenated in the presence of a 5% palladium-on-carbon catalyst. Hydrogenation stops upon consumption of 1360 ml of hydrogen. 1.4 ml of benzyl chloride are added and the hydrogenation is continued until completion. The catalyst is removed by filtration and the filtrate is processed in a manner analogous to that described in Example 1(B). The product obtained is identical with the product obtained in Example 1(B).

The 2,3,4-tribenzyloxy-benzyl-hydrazine hydrochloride aforesaid can be obtained as follows: 2,3,4-tribenzyloxy-benzaldehyde is condensed with formyl-hydrazine in ethanol, the resulting hydrazone is reduced by means of sodium amalgam in aqueous ethanol to form N^1-(2,3,4-tribenzyloxy)-benzyl-N^2-formyl-hydrazine from which the formyl group is split off by treatment with methanolic hydrochloric acid.

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-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 58.25 mg of mannitol and 23.7 mg of polyvinyl-pyrrolidone.

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

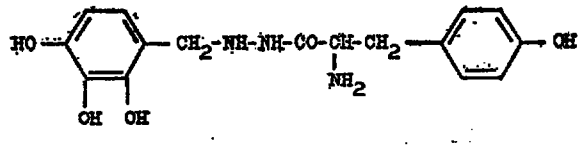
Example B

Tablets containing N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride as the active ingredient are manufactured in the usual manner, each tablet containing 150 mg of said hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinyl-pyrrolidone, 1.5 mg of magnesium stearate, and 13.5 mg of talc.

These tablets are administered about 30—60 minutes before 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 which are also manufactured in the usual manner.

WHAT WE CLAIM IS:—

1) The compound of the formula



(I)

and acid addition salts thereof.

2) N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide and acid addition salts thereof.

3) N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride.

4) 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

formed. The crystals obtained after trituration of this mass was *iso*propanol and crystalization are washed with *iso*propanol and ether. N^1-*L*-tyrosine-N^2-(2,3,4-tribenzyloxy-benzylidene)-hydrazide acetate with a melting point of 143°—145° C. is obtained.

EXAMPLE 3

A mixture of 13.4 g of *L*-N-carbobenzoxy-O-benzyl-tyrosine and 15.9 g of 2,3,4-tribenzyloxy-benzyl-hydrazine hydrochloride is added to 300 ml of methylene chloride, stirred and treated with 4.6 ml of triethylamine. 6.7 g of N,N'-di*cyclo*hexyl-carbodiimide are added and stirring is continued for 1 hour. The di*cyclo*hexylurea precipitate is removed by filtration and the methylene chloride solution is washed 2—3 times with water, dried over sodium sulfate and concentrated under reduced pressure. Crystallization occurs on dilution with ether. The *L*-N-carbobenzoxy-O-benzyl-tyrosine-(2,3,4-tribenzyloxy)-benzyl-hydrazide thus obtained melts at 153°—154° C.

9.8 g of the hydrazide obtained according to the preceding paragraph are suspended in 200 ml of methanol and hydrogenated in the presence of a 5% palladium-on-carbon catalyst. Hydrogenation stops upon consumption of 1360 ml of hydrogen. 1.4 ml of benzyl chloride are added and the hydrogenation is continued until completion. The catalyst is removed by filtration and the filtrate is processed in a manner analogous to that described in Example 1(B). The product obtained is identical with the product obtained in Example 1(B).

The 2,3,4-tribenzyloxy-benzyl-hydrazine hydrochloride aforesaid can be obtained as follows: 2,3,4-tribenzyloxy-benzaldehyde is condensed with formyl-hydrazine in ethanol, the resulting hydrazone is reduced by means of sodium amalgam in aqueous ethanol to form N^1-(2,3,4-tribenzyloxy)-benzyl-N^2-formyl-hydrazine from which the formyl group is split off by treatment with methanolic hydrochloric acid.

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-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride, 58.25 mg of mannitol and 23.7 mg of polyvinyl-pyrrolidone.

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

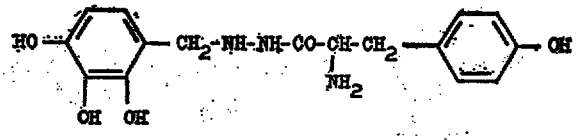
Example B

Tablets containing N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride as the active ingredient are manufactured in the usual manner, each tablet containing 150 mg of said hydrochloride, 200 mg of mannitol, 120 mg of corn starch, 15 mg of polyvinyl-pyrrolidone, 1.5 mg of magnesium stearate, and 13.5 mg of talc.

These tablets are administered about 30—60 minutes before 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 which are also manufactured in the usual manner.

WHAT WE CLAIM IS:—

1) The compound of the formula



(I)

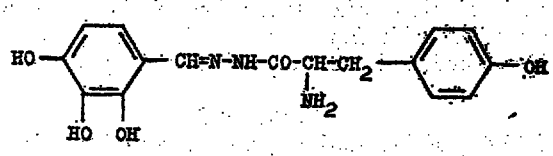
and acid addition salts thereof.

2) N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide and acid addition salts thereof.

3) N^1-*L*-tyrosine-N^2-(2,3,4-trihydroxybenzyl)-hydrazide hydrochloride.

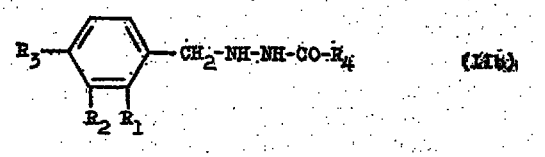
4) A process for the manufacture of the benzyl-hydrazide derivatives claimed in claim 1, which process comprises *either* hydrogenating the benzylidene-hydrazide of the formula

* C L M S *



(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 α-amino-β-(*p*-hydroxyphenyl)-ethyl group in a compound of the general formula



(IIIa)

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 α-amino-β-(*p*-hydroxyphenyl)-ethyl group or a group (as hereinbefore defined) convertible into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group, at least one of the substituents R_1, R_2, R_3, R_4 and R_5 being different from the hydroxy group or from the α-amino-β-(*p*-hydroxyphenyl)-ethyl group, or in an acid addition salt of such a compound, into the hydroxy group and/or into the α-amino-β-(*p*-hydroxyphenyl)-ethyl group *and*, if desired, splitting a racemate obtained into the optical antipodes and, also if desired, converting a base obtained into an acid addition salt.

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

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

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

8) A process according to any one of claims 4 to 7 inclusive, wherein the antipode derived from *L*-tyrosine is isolated.

9) A process as claimed in claim 4 for the manufacture of the benzyl-hydrazide derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1—3.

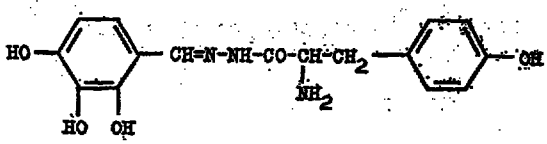
10) Benzyl-hydrazide derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 4 to 9 inclusive.

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

12) A pharmaceutical preparation according to claim 11, wherein *L*-dopa or an acid addition salt thereof is also present.

13) A pharmaceutical preparation according to claim 12, wherein the quantitative ratio of the benzyl-hydrazide derivative to *L*-dopa is 0.5—2 parts by weight of said benzyl-hydrazide derivative per part by weight of *L*-dopa.

14) The benzylidene-hydrazide of the formula



(IIa)

and its acid addition salts.

* C L M S *

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