# PATENT SPECIFICATION

NO DRAWINGS

**920,623**

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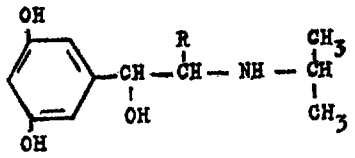
**International Classification:—C07c.**

COMPLETE SPECIFICATION

## Substituted Amino-Alcohols

We, ERNST BOEHRINGER, ILSE LIEBRECHT, JULIUS LIEBRECHT, WALTER MAYER-LIST, WILHELM DIRIK BOEHRINGER and HERMANN ALBERT BOEHRINGER all German citizens trading in partnership as C. H. BOEHRINGER SOHN of Ingelheim am Rhein, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with the production of new compounds of the formula

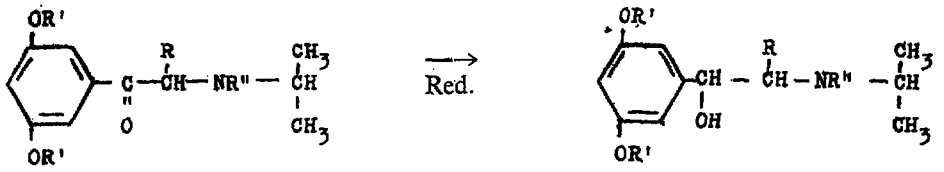


I

(in which R is a hydrogen atom or a methyl group) and acid-addition salts thereof.

The new compounds according to the invention may be produced by the following processes:

1. Reduction of a compound of the formula II according to the following reaction scheme:



II III

where $R^1$ is hydrogen or a group readily replaceable by hydrogen, such as for example an acyl, aralkyl or alkyl group, $R^{11}$ is hydrogen or an aralkyl residue and R has the above stated meaning, followed by any necessary replacement of $R^1$ and $R^{11}$ by hydrogen atoms.

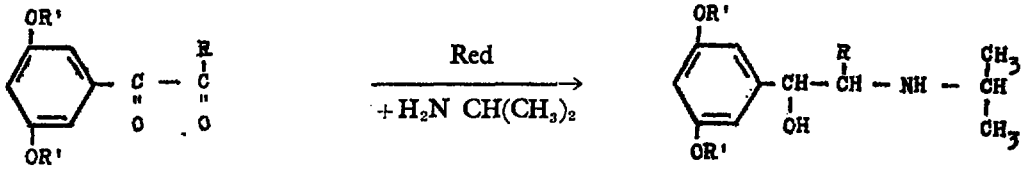
The reduction can be carried out for example by catalytic reduction, e.g. with Raney nickel or with palladised charcoal; chemical reduction, for example, with lithium/aluminium hydride or sodium borohydride can also be used.

If in the above indicated formula III $R^1$ is an alkyl residue, this can be replaced by hydrogen by ether-splitting agents, for example, by heating with hydrogen halides; in this case the alcoholic hydroxyl group is advantageously protected by acetylation, and the splitting carried out using hydrobromic acid in anhydrous glacial acetic acid or glacial acetic acid/acetic anhydride. If in the above formula III $R^1$ signifies an acyl residue, this can be split off by treatment with acids. If $R^1$ and $R^{11}$ are an aralkyl residue, this can be removed by hydrogenolysis.

The compounds of the general formula II, used as starting material in this process can be obtained in any desired way, for example by substitution of the halogen atom of a

1 - (3,5 - dialkoxyphenyl) - 1 - oxo - 2-halogen ethane or propane by the isopropylamino group.

2. Reduction of a diketo compound of the general formula IV in the presence of isopropylamine according to the following reaction scheme:

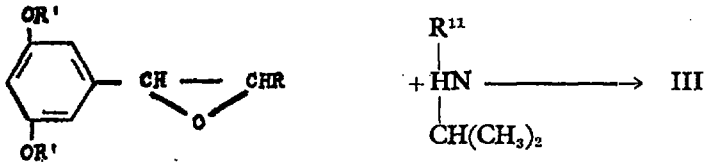



IV V

where R and $R^1$ have the above stated meanings.

The reduction can for example, be carried out by catalytic reduction with Raney nickel or with palladised charcoal. In the compound V so obtained, the residue $R^1$ is, if necessary, replaced by hydrogen, as described under process 1.

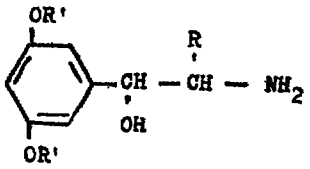
3. Reaction of a compound of the formula VI with isopropylamine or secondary amines according to the following reaction scheme:




VI

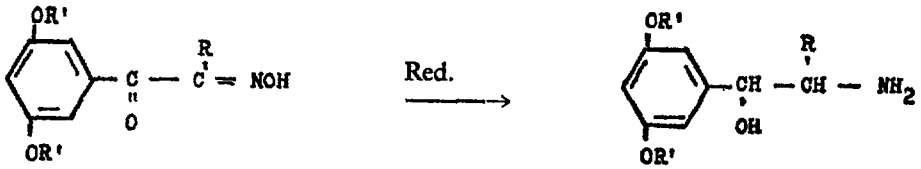
R, $R^1$ and $R^{11}$ have the above stated meanings. The reaction can be carried out in the usual manner, for example at temperatures between 0 and 100°C, preferably at 10—30°C in aqueous alcoholic solution. The replacement of $R^1$ and $R^{11}$ by hydrogen can be effected as described under process 1.

4. Introduction of the isopropyl group into compounds of the general formula



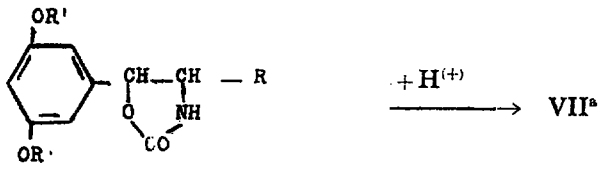

VII

in which R and $R^1$ have the above stated meanings, which compounds can be obtained for example by reduction of an isonitroso ketone of the general formula




VIII VII[a]

or by acid-splitting of an oxazolidone-2-compound of the general formula



IX

The replacement of $R^1$ by hydrogen can be effected as described under Process 1. The introduction of the isopropyl group can be effected for example by reaction of the primary amine of the Formula VII with acetone, and catalytic reduction of the intermediate Schiff's base to the compound I.

The new compounds according to the invention can be separated into their optically active components by any desired method e.g. by fractional crystallisation of their salts with optically active acids, such as dibenzoyl- or ditoluoyl-α-tartaric acid.

The new 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino ethane or propane are distinguished by a very good broncholytic effect and influence valvular disturbances of the heart in particularly favourable manner. Compared to known, analogous compounds, for example the known 1-(3,4-dihydroxyphenyl)-derivatives, they distinguish themselves in both fields of indication by a better compatibility and a longer lasting effect. With peroral application, they are better absorbed and they are more easily administered. Furthermore they possess improved stability and are therefore more readily manufactured and more easily stored.

The new compounds according to the invention may be administered in the form of salts with physiologically acceptable acids. Suitable acids which may be used are, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, maleic, tartaric, citric or succinic acid.

The new compounds according to the invention, or their salts may be formulated into pharmaceuticals together with a pharmaceutical carrier or excipient; such compositions may be designed for oral, nasal, rectal or parenteral administration.

Compositions for oral administration may be liquid, syrupy or solid. Thus, for example, the compounds according to the invention may be made up in an aqueous medium in the form of suspension, emulsion or like formulation, said formulation also containing, if desired, such adjuvants as suspending agents, dispersing agents, flavouring agents and/or sweetening agents. One may also with advantage prepare solid formulations, for example powders, capsules or dragees, in which the compounds according to the invention are in association with a solid carrier. In particular one may also provide tablets containing the active compounds, in which the compounds are in association with suitable tabletting adjuvants, for example, sugars, e.g. lactose or sucrose, lubricants, e.g. magnesium stearate and/or binders, e.g. starch.

Where the compositions are intended for rectal administration, the pharmaceutical carrier will generally include a suppository base such as a glyceride.

Compositions for nasal administration may take the form of inhalations or sprays.

In compositions for parenteral administration the pharmaceutical carrier is preferably sterile, pyrogen-free water or a parenterally acceptable oil, and may include dispersing or suspending agents and/or physiological salts.

In order that the invention may be well understood, the following examples are given by way of illustration only:

EXAMPLE 1

1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2 - isopropylamino - ethane sulphate

59 g. of 1 - (3,5 - dihydroxy - phenyl)-2 - isopropylamino - ethanone were dissolved in 590 ml. of methanol and hydrogenated under pressure (5 atm) at room temperature in the presence of about 80 g. of Raney nickel. The absorption of hydrogen was completed after a few minutes. After filtering off the catalyst with suction, the calculated amount of 20% alcoholic sulphuric acid was added to the filtrate. The precipitated crystallisate was filtered off and washed with alcohol. For purification, the sulphate was dissolved in water and filtered over iron-free carbon. The filtrate was then evaporated *in vacuo*, and the residue taken up in alcohol. The precipitate which crystallised out after standing was filtered with suction and washed with alcohol. After recrystallising from 90% alcohol, 61 g. (83.2% of the theory) of 1-(3,5 - dihydroxyphenyl) - 2 - isopropylamino-ethanol sulphate were obtained. M.pt. = 202—203°C.

For the preparation of the free base, the substance was dissolved in a little water and neutralised with aqueous ammonia. The crystalline precipitate which separated after standing was filtered off with suction and

washed with water. M.pt. of the free base 100°C.

EXAMPLE 2

1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2 - isopropylamino - ethane hydrobromide

a) 3,5-dimethoxyphenyl-glyoxal

11.2 g. of selenium dioxide were dissolved at 50—60°C in 60 ml. of dioxan and 2 ml. of water. 18 g. of 3,5-dimethoxy-acetophenone were then added, and the mixture heated at 100°C on a water bath for 8 hours, allowed to stand at room temperature overnight, filtered off from the separated selenium, filtered with suction over charcoal and concentrated *in vacuo*. Water was poured over the residue which was occasionally stirred until the initially brown oil had completely crystallised. The oil was recrystallised from dioxan/petroleum ether: m.pt. = 92°C, yield 16.0 g. = 75% of the theory.

b) 1 - (3,5 - dimethoxyphenyl) - 1 - hydroxy-isopropylamino - ethane hydrochloride

2 g. of 3,5 - dimethoxyphenyl - glyoxal and 7 g. of isopropylamine in 80 ml. of methanol were maintained for half an hour at 45—50°C and then hydrogenated under normal conditions with Raney nickel. Almost 2 mol. hydrogen were taken up. After filtering with suction from the catalyst and distilling *in vacuo* the residue was taken up in ether. The hydrochloride can be precipitated with ethereal hydrochloric acid and recrystallised from methyl ethyl ketone/ether. Yield 1.7 g. = 65.5% of the theory, m.pt. = 146°C.

c) 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2-isopropylamino-ethane hydrobromide

7 g. of 1 - (3,5 - dimethoxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane hydrochloride and 70 ml. of acetic anhydride were heated for one hour under reflux on an oil bath. The reaction mixture was cooled, and 25 ml. of 66% hydrobromic acid added slowly with cooling at 20°C and the mixture heated on an oil bath under reflux for a further hour (interior temperature 105°C). After cooling, 70 ml. of acetic anhydride were added with cooling at 20°C and then slowly 25 ml. of 66% hydrobromic acid, and the mixture again heated for one hour and under reflux on an oil bath (interior temperature 105°C). The acid was distilled off from the reaction mixture in vacuo. 100 ml. of 5% hydrobromic acid were added to the residue which was warmed for one hour on a boiling water bath. Charcoal was then added, the solution filtered with suction and the filtrate concentrated *in vacuo*. The residue crystallised after inoculation in glacial acetic acid, the acetic acid was filtered off and the residue washed with a mixture of acetone/ether (1:1). After evaporating the mother liquor, crystallisation again takes place. For recrystallisation the substance was dissolved in a little hot *n*-butanol, filtered with suction over charcoal and then slowly precipitated with ether. Yield 3.5 g. = 62.8% of the theory. M.pt. of the hydrobromide 184°C.

EXAMPLE 3

1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2 - isopropylamino - ethane hydrobromide

a) 1 - (3,5 - dimethoxyphenyl) - 1 - hydroxy-2-bromoethane

50.5 g. of 3,5 - dimethoxy - ω - bromo-acetophenone, 126 g. of aluminium isopropoxide and 525 g. of isopropanol were heated under reflux with stirring for 3½ hours; the isopropanol was extensively distilled off and 200 ml. water added to the residue. The aqueous solution was extracted with ether, the ethereal phase dried and distilled. Yield 30 g. = 59.5% of the theory, b.pt. 143°C/0.1 mm.

b) 3,5-dimethoxyphenyl-ethylene oxide

A mixture of 28.5 g. of 1-(3,5-dimethoxyphenyl) - 1 - hydroxy - 2 - bromo - ethane, 8.95 g. potassium hydroxide in 75 ml. of alcohol and 50 ml. of alcohol was stirred at room temperature for 15 minutes. 500 ml. of water were then added and the epoxide extracted with ether. The ethereal solution was washed thrice with water, dried over potassium carbonate and distilled. Yield 16 g. = 81.5% of the theory, b.pt. 112—114°C/0.5 mm.

c) 1 - (3,5 - dimethoxyphenyl) - 1 - hydroxy-2-isopropylamino-ethane hydrochloride

5 g. of 3,5 - dimethoxyphenyl - ethylene oxide, 9.9 g. of isopropylamine and 100 ml. of alcohol were heated in an autoclave at 70°C for 5 hours and concentrated. The residue was dissolved in methanol and precipitated with ethereal hydrochloric acid. It was recrystallised from methanol/ether. Yield 5.1 g. = 66.5% of the theory, m.pt. = 147°C.

d) 1 - (dihydroxyphenyl) - 1 - hydroxy - 2-isopropylamino - ethane hydrobromide was prepared as indicated in Example 2c).

EXAMPLE 4

Optical resolution of 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy - 2 - isopropylamino-ethane

95 g. of di - *p* - toluoyl - tartaric acid were heated under reflux with 52.3 g. of the racemic base in 400 ml. of 50% *iso*-propanol for half an hour, until the solution was clear and

then crystallised. 92 g. of product, m.pt. = 163—164°C, were obtained. $[\alpha]_D = -89.6°$ (5% in methanol).

This product was recrystallised from 50% *iso*-propanol until the rotation and melting point remained constant (3 times). $[\alpha]_D = -73.6°$; m.pt. = 165—166°C.

32.5 g. of this di-*p*-toluoyl-tartaric acid salt were dissolved in 150 ml. of ethanol with warming, 32 ml. of 21% ethanolic hydrochloric acid added, and then 700 ml. of ether. By dissolving once more and precipitating with ether, (+) −1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy - 2 - isopropylamino-ethane hydrochloride m.pt. = 212—213°C, $[\alpha]_D = +45.2°$ (5% in methanol) was obtained. The mother liquor of the first crystallisation was evaporated to dryness and yields 45 g. of crystals, $[\alpha]_D = -112°$ (5% in methanol). The hydrochloride of the dextrorotatory isomer was produced analogously. M.pt. = 212°C, $[\alpha]_D = -45.0°$ (5% in methanol).

EXAMPLE 5

1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2 - isopropylamino - propane hydrochloride

a) 1 - (3,5 - dimethoxyphenyl) - 1 - oxo-2 - isopropylamino - propane hydrochloride

39 g. of 3,5 - dimethoxypropiophenone were dissolved in 400 ml. of ether, and 10.2 ml. of bromine added dropwise with stirring at −10°C. The ether was removed *in vacuo*, and a solution of 30 g. of isopropylamine in 100 ml. of benzene added to the residue which was heated under reflux for 1 hour. The separated salt was filtered off with suction, and the benzene solution shaken twice with water. After drying over sodium sulphate, ethereal hydrogen chloride solution was added to precipitate the hydrochloride of 1-(3,5-dimethoxyphenyl) - 1 - oxo - 2 - isopropylamino-propane, which was recrystallised from methanol. Yield 27.5 g. = 48% of theory, m.pt. = 232°C.

b) 1 - (3,5 - dihydroxyphenyl) - 1 - oxo-2 - isopropylamino - propane hydrobromide

32 g. of 1 - (3,5 - dimethoxyphenyl) - 1-oxo - 2 - isopropylaminopropane - hydrochloride were heated under reflux for 2 hours with 320 ml. of 48% hydrogen bromide solution. The reaction solution was then treated with active charcoal and the solvent removed in vacuo. The residue was recrystallised from iso-propanol. Yield 23 g. = 68% of theory, m.pt. = 201°C.

c) 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2 - isopropylamino - propane hydrochloride

10 g. of 1 - (3,5 - dihydroxyphenyl) - 1-oxo - 2 - isopropylamino - propane hydrobromide were dissolved in 100 ml. of methanol and catalytically hydrogenated in the presence of Raney nickel under ambient conditions. When the hydrogen uptake was completed, the solvent was removed *in vacuo*, the residue taken up in water, and the 1-(3,5-dihydroxyphenyl) - 1 - hydroxy - 2 - isopropylamino-propane precipitated in the form of the free base by addition of aqueous ammonia. M.pt. = 144—145°C.

The free base was dissolved in a little ethanol and 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - propane hydrochloride precipitated by addition of ethanolic hydrogen chloride. After twice recrystallising from ethanol, m.pt. = 217—218°C., yield 6.4 g. = 75% of theoretical.

EXAMPLE 6

Tablets

Each tablet contains:—

| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropyl-amino-ethane-sulphate | 5.0 mg. |
| Lactose, pulv. | 35.4 mg. |
| Maize starch, dried | 33.0 mg. |
| Finely dispersed silica | 5.6 mg. |
| Polyvinyl pyrrolidone | 0.6 mg. |
| Magnesium stearate | 0.4 mg. |
| ~~Table~~ weight | 80.0 mg. |

Tablet

5.0 g. of 1 - (3,5 - Dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane sulphate were mixed with 35.4 g. powdered lactose, 25.0 g. of dried maize starch and 4.0 g. finely dispersed silica, triturated with a 5% alcoholic solution of 0.6 g. polyvinyl pyrrolidone and passed through a screen of 1 mm. mesh. The granulate was dried for about 24 hours in an air oven at about 60°C and again passed through a screen of 1 mm. mesh.

70.0 g. of the prepared granulate were combined in a mixer with a mixture of 1.6 g. finely dispensed silica, 8.0 g. of dried maize starch and 0.4 g. magnesium stearate, which had been passed through a screen of 0.3 mm. The mixture was pressed into about 1,000 tablets, each weighing 80 mg.

EXAMPLE 7

2% Solution for inhalation

1 10 ml. bottle contains:

| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropylaminoethane sulphate | 200 mg. |
| Sodium pyrosulphite | 1 mg. |
| Disodium salt of ethylenediaminetetraacetic acid | 5 mg. |
| N/10 HCl to pH 3 | |
| Demineralised water | to 10 ml. |

Clear, Colourless solution of pH 3.

EXAMPLE 8

Ampoules

Each ampoule contains:—

| | |
|---|---|
| 1-(3,5-dihydroxyphenyl)-1-hydroxy-2-isopropylamino ethane sulphate | 0.5 m.g. |
| Sodium pyrosulphite | 0.1 mg. |
| Disodium salt of ethylenediaminetetraacetic acid | 0.5 mg. |
| Sodium chloride p.a. | 8.0 mg. |
| N/10 HCl to pH 3.5 | |
| Distilled water | to 1.0 ml. |

EXAMPLE 9

Suppositories

Each suppository contains:—

| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropyl-amino-ethane sulphate | 5.1 mg. |
| Lactose, pulv. | 45 mg. |
| Suppository base | to 1.7 g. |

0.5 g. 1 - (3,5 - Dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane sulphate were thoroughly ground together with 4.5 g. powdered lactose and homogeneously dispersed in 165 g. molten suppository base and the mixture filled into suppository moulds: 100 suppositories, each containing 5 mg. of 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2-isopropylamino-ethane sulphate.

EXAMPLE 10

Powder

1 g. powder contains:—

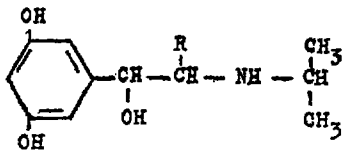
| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropyl-amino-ethane sulphate | 5 mg. |
| Lactose | 495 mg. |
| Maize starch | 500 mg. |

49.5 g. of lactose were mixed portionwise with 0.5 g. of 1 - (3,5 - dihydroxyphenyl)-1 - hydroxy - 2 -isopropylamino - ethane sulphate and the mixture combined with 50 g. of maize starch. The mixture was filled into capsules in 1 g. portions.

Each capsule contains *ca.* 5 mg. 1-(3,5-dihydroxyphenyl) - 1 - hydroxy - 2 - isopropyl-amino-ethane sulphate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



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(in which R is a hydrogen atom or a methyl group) and their salts with physiologically acceptable acids.

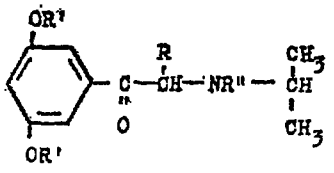
2. 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane and its physiologically acceptable acid-addition salts.

3. 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - propane and its physiologically acceptable acid-addition salts.

4. Compounds as claimed in any of claims 1—3 in the form of salts with hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, maleic, tartaric, citric or succinic acid.

5. Compounds as claimed in any of claims 1 to 4 substantially as herein described.

6. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



II

EXAMPLE 9

Suppositories

Each suppository contains:—

| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropyl-amino-ethane sulphate | 5.1 mg. |
| Lactose, pulv. | 45 mg. |
| Suppository base | to 1.7 g. |

0.5 g. 1 - (3,5 - Dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane sulphate were thoroughly ground together with 4.5 g. powdered lactose and homogeneously dispersed in 165 g. molten suppository base and the mixture filled into suppository moulds: 100 suppositories, each containing 5 mg. of 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy-2-isopropylamino-ethane sulphate.

EXAMPLE 10

Powder

1 g. powder contains:—

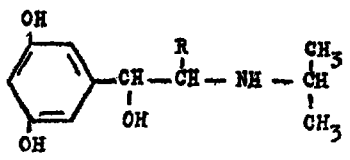
| | |
|---|---|
| 1-(3,5-Dihydroxyphenyl)-1-hydroxy-2-isopropyl-amino-ethane sulphate | 5 mg. |
| Lactose | 495 mg. |
| Maize starch | 500 mg. |

49.5 g. of lactose were mixed portionwise with 0.5 g. of 1 - (3,5 - dihydroxyphenyl)-1 - hydroxy - 2 -isopropylamino - ethane sulphate and the mixture combined with 50 g. of maize starch. The mixture was filled into capsules in 1 g. portions.

Each capsule contains *ca.* 5 mg. 1-(3,5-dihydroxyphenyl) - 1 - hydroxy - 2 - isopropyl-amino-ethane sulphate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



I

(in which R is a hydrogen atom or a methyl group) and their salts with physiologically acceptable acids.

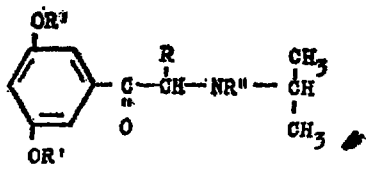
2. 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - ethane and its physiologically acceptable acid-addition salts.

3. 1 - (3,5 - dihydroxyphenyl) - 1-hydroxy - 2 - isopropylamino - propane and its physiologically acceptable acid-addition salts.

4. Compounds as claimed in any of claims 1—3 in the form of salts with hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, maleic, tartaric, citric or succinic acid.

5. Compounds as claimed in any of claims 1 to 4 substantially as herein described.

6. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



II

* C L M S *

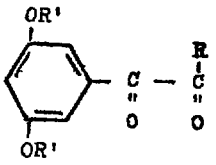
(in which $R^1$ is a hydrogen atom or a group readily replaceable by hydrogen, $R^{11}$ is hydrogen or an aralkyl residue and R has the meaning given in claim 1) is reduced whereafter $R^1$ and $R^{11}$ are, if necessary, replaced by hydrogen atoms.

7. A process as claimed in claim 6 in which the reduction is carried out by hydrogenation in the presence of a hydrogenation catalyst.

8. A process as claimed in claim 7 in which the catalyst is Raney nickel or palladised charcoal.

9. A process as claimed in claim 6 in which the reduction is carried out with lithium aluminium hydride or sodium borohydride.

10. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



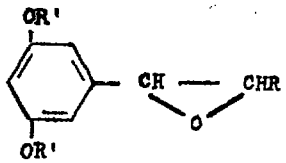
IV

(in which $R^1$ has the meaning given in claim 6 and R has the meaning given in claim 1) is reduced in the presence of iso-propylamine whereafter $R^1$ is if necessary replaced by a hydrogen atom.

11. A process as claimed in claim 10 in which the reduction is carried out by hydrogenation in the presence of a hydrogenation catalyst.

12. A process as claimed in claim 11 in which the catalyst is Raney nickel or palladised charcoal.

13. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



VI

(in which $R^1$ has the meaning given in claim 6 and R has the meaning given in claim 1) is reacted with an amine of the general formula

$$R^{11}—NH—CH(CH_3)_2$$

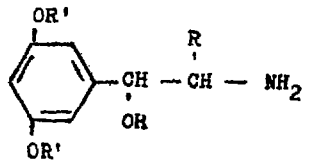
(in which $R^{11}$ has the meaning given in claim 6) whereafter $R^1$ and $R^{11}$ are if necessary replaced by hydrogen atoms.

14. A process as claimed in claim 13 in which the reaction is carried out at a temperature between 0 and 100°C.

15. A process as claimed in claim 14 in which the reaction is carried out at a temperature between 10 and 30°C.

16. A process as claimed in any of claims 13 to 15 in which the reaction is carried out in aqueous alcoholic medium.

17. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



VII

(in which R has the meaning given in claim 1 and $R^1$ has the meaning given in claim 6) is isopropylated, whereafter $R^1$ is, if necessary, replaced by a hydrogen atom.

18. A process as claimed in claim 17 in which a compound of general formula VII is reacted with acetone and the resulting Schiff's base is reduced.

19. A process as claimed in claim 18 in which the reduction is carried out with hydrogen in the presence of a hydrogenation catalyst.

20. A process as claimed in any of claims 6 to 19 in which the compounds of general formula I given in claim 1 are resolved into their optical isomers.

21. A process as claimed in claim 20 in which the resolution is carried out by means of fractional crystallisation of optically active salts with optically active acids.

22. A process as claimed in claim 21 in which the acid is dibenzoyl- or ~~ditoluol-~~ ditoluoyl-α-tartaric acid.

23. A process as claimed in any of claims 6 to 22 substantially as herein described.

24. A process as claimed in any of claims 6 to 22 substantially as herein described with reference to examples 1 to 5.

25. Compositions for oral, nasal, rectal or parenteral administration containing one or more of the compounds as claimed in claim 1 together with a pharmaceutical carrier or excipient.

26. Compositions as claimed in claim 25 in the form of suspensions, emulsions, syrups, powders, tablets, capsules, or dragees, sprays, inhalations, suppositories or injectable solutions.

27. Compositions as claimed in claim 25 in which the carrier or excipient includes a tabletting adjuvant, flavouring or suspending

* C L M S *

or dispersing agents, sterile pyrogen free water, oil or oily emulsions or suppository bases.

28. Compositions as claimed in any of claims 25 to 27 substantially as herein described.

29. Compositions as claimed in any of claims 25 to 27 substantially as herein described with reference to examples 6 to 10.

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