

PATENT SPECIFICATION

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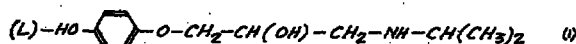
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(54) A NEW 1-PHENOXY-3-ISOPROPYLAMINO-2-PROPANOL AND PROCESSES FOR THE PRODUCTION THEREOF

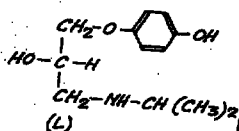
(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to (L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)propane of formula I

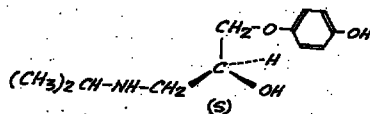


as well as to processes for the production thereof.

The Fischer projection of formula I has the following appearance:



and corresponds to the (S)-form in the Cahn-Ingold- and Prelog-nomenclature:



The new compound has valuable pharmacological properties, particularly an effect on adrenergic β -receptors. It stimulates specifically cardiac β -receptors. In particular, it has a positively inotropic and chronotropic action on the isolated vestibule of the heart of the guinea pig in a concentration range of from 0.005 to 0.5 $\mu\text{g/ml}$, and on the anaesthetised cat in a dosage range of 0.001 to 0.1 mg/kg, intravenously. As is shown from tests on the anaesthetised cat, the new compound, however, causes, when administered in doses which clearly have a positively inotropic and chronotropic action, no, or only a slight, decrease in the arterial blood pressure, i.e. it stimulates specifically the cardiac β -receptors in comparison with the β -receptors in the blood vessels, and consequently clearly differs qualitatively from isoproterenol, which strongly stimulates the β -receptors of the heart and of the blood vessels. Since, however, a decrease in blood pressure leads, by reflex action, to a tachycardia, it can be assumed that the new compound, when administered to humans in doses which have an equally strong positively inotropic action, produces a tachycardia which is appreciably less than that caused by isoproterenol.

To be particularly emphasised also is the fact that the new compound is effective on the anaesthetised cat for considerably longer than isoproterenol is, and, moreover, that it produces clear effects also after intraduodenal administration of 0.05 mg/kg.

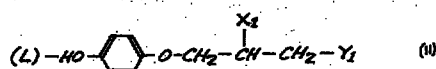
The new compound can hence be used, alone or in combination with other

preparations, such as heart glycosides, as an agent having a positively inotropic action, especially for the treatment of myocardial insufficiency. Administration of the new compound in the form of suitable pharmacological preparations can be effected orally in doses of 1 to 25 mg per single dose, and intravenously in doses of 1 to 20 mcg/kg as a single dose, or in doses of 0.2 to 2.0 mcg/kg/minute as an intravenous drip.

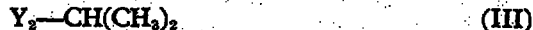
(L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane is obtained by processes known per se. Thus, the new compound can be obtained by a process in which (D,L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropyl-amino)-propane is split off, and (L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane is optionally isolated in the form of a salt. The splitting off and isolation are performed in a manner known per se. For example, the racemate can be converted with salt-forming, optically active acids, such as organic carboxylic or sulphonic acids, e.g. the (D)- and (L)-forms of tartaric acid, di-o-toluytartaric acid, malic acid, mandelic acid, camphorsulphonic acid, quinic acid, lactic acid, glutamic acid or aspartic acid, into acid addition salts. The resulting mixtures can, by virtue of physical-chemical differences, e.g. solubility, crystallisability, etc., be separated into the diastereoisomeric salts and, optionally, the optically active L-form can be liberated from the salt.

It is also possible to split off the (L)-form from the racemate by fractional crystallisation from a suitable solvent, optionally from an optically active solvent, or by chromatography, especially thin-layer chromatography, on an optically active carrier substance.

The new compound can be obtained also by the reaction of a compound of formula II



with a compound of formula III

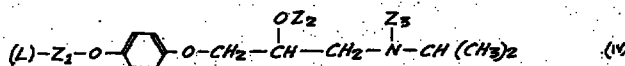


wherein one of the radicals Y_1 and Y_2 is amino $-NH_2$ and the other is a reactive esterified hydroxy group, and X_1 represents hydroxy, or Y_1 together with X_1 forms an epoxy group, whereby in the latter case the absolute configuration of the epoxide corresponds to the (S)-form and Y_2 is $-NH_2$.

A reactive esterified hydroxyl group is, in particular, a hydroxyl group esterified by a strong inorganic or organic acid, especially a hydrohalic acid such as hydrochloric acid, hydrobromic acid or hydriodic acid, also sulphuric acid or a strong organic sulphonic acid such as a strong aromatic sulphonic acid, for example benzene-sulphonic acid, 4-bromobenzenesulphonic acid or 4-toluenesulphonic acid. Thus, Y_1 and Y_2 stand, in particular, for chlorine, bromine or iodine.

This reaction is performed in the usual manner. With the use of a reactive ester as starting material, the process is carried out preferably in the presence of a basic condensing agent and/or with an excess of amine. Suitable basic condensing agents are, for example, alkali hydroxides such as sodium or potassium hydroxide, alkali carbonates such as potassium carbonate, and alkali alcoholates such as sodium methylate, potassium ethylate and potassium tertiary butylate.

Furthermore, the new compound can be obtained by a process in which in a compound of formula IV



wherein at least one of the radicals Z_1 , Z_2 and Z_3 stands for a group that can be split off, and the remaining radical(s) stand(s) for hydrogen, the group(s) Z_1 and/or Z_2 and/or Z_3 is (are) split off.

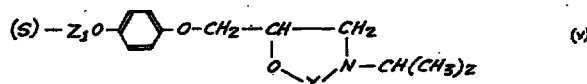
Such radicals that can be split off are, in particular, radicals that can be split off by solvolysis, reduction, pyrolysis or fermentation. Radicals that can be split off by solvolysis, are, in particular, radicals that can be split off by hydrolysis, alcoholysis or acidolysis. Radicals Z_1 that can be split off by hydrolysis are, e.g. acyl radicals, such as optionally functionally modified, especially esterified, carboxyl groups, such as alkoxy-carbonyl radicals, e.g. the tert.butoxycarbonyl radical or the ethoxycarbonyl radical, aralkoxycarbonyl radicals such as phenyl-lower-alkoxycarbonyl radicals, e.g. a carbobenzoxy radical, halocarbonyl radicals, e.g. the chlorocarbonyl radical, also

arylsulphonyl radicals such as toluenesulphonyl radicals or bromobenzene sulphonyl radicals, and optionally halogenated, such as fluorinated, lower alkanoyl radicals, e.g. the formyl, acetyl or trifluoroacetyl radical, or a benzoyl radical, also those which together with the oxygen atom form a etherified hydroxy group, such as sugar radicals, e.g. a 1-aldopentosidyl radical or a 1-aldohexosidyl radical, such as the 1-glucopyranosidyl radical, or lower alkyl radicals, e.g. the methyl or ethyl radical, or lower alkenyl radicals such as the allyl or methallyl radical, or phenyl-lower-alkyl radicals, e.g. the benzyl radical.

Groups Z_2 that can be split off by hydrolysis are, e.g., the groups mentioned above for Z_1 , whereby, if Z_2 stands for an acyl group Z_3 cannot represent hydrogen.

Groups Z_3 that can be split off by hydrolysis are, for example, acyl radicals, such as the above-mentioned, or also cyano groups or silyl radicals, such as the trimethylsilyl radical. Radicals Z_3 that can be split off by hydrolysis are, besides the mentioned radicals, also doubly bound radicals, e.g. an alkylidene or benzyldiene radical, or a phosphoranylidene group, such as the triphenyl phosphoranylidene group, whereby then the nitrogen atom carries a positive charge.

Compounds having radicals that can be split off by hydrolysis are, for example, also compounds of formula V



wherein Z_1 represents hydrogen or has the above-given meanings, and Y stands for the carbonyl or thiocarbonyl radical, or particularly for a bivalent radical Y_3 of an aldehyde or ketone of the formula $Y_3=O$, e.g., di-lower-alkyl ketones such as methyl ethyl ketone or acetone. Aldehydes $Y_3=O$ are, e.g., lower alkanols such as acetaldehyde or formaldehyde, also benzaldehyde.

The hydrolysis is performed in the usual manner, e.g. in the presence of hydrolysing agents, e.g. in the presence of acid agents, such as an aqueous mineral acid such as sulphuric acid, or hydrohalic acid such as hydrochloric or hydrobromic acid, or in the presence of an organic acid, e.g. a suitable carboxylic acid, such as an α -haloalkancarboxylic acid, e.g. of a trifluoro- or chloroacetic acid, of an organic sulphonc acid, e.g. benzene- or toluenesulphonic acid, or in the presence of acid ion exchangers, or of basic agents, e.g. alkali hydroxides, such as sodium hydroxide. Oxycarbonyl radicals, arylsulphonyl radicals and cyano groups can be split off in an advantageous manner by an acid medium such as a hydrohalic acid. Particularly suitable in this case is, for example, the splitting-off by means of aqueous hydrochloric acid, optionally in admixture with acetic acid. Furthermore, it is possible to split off, e.g., a tert.-butoxycarbonyl radical, under anhydrous conditions, by treatment with a suitable acid, such as trifluoroacetic acid.

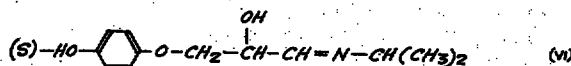
Radicals Z_1 and/or Z_2 and/or Z_3 that can be split off by reduction are, for example, α -arylalkyl radicals such as benzyl radicals, or α -aralkoxycarbonyl radicals such as benzyloxycarbonyl radicals; these can be split off in the usual manner by hydrogenolysis, especially by catalytically activated hydrogen, such as by hydrogen in the presence of a hydrogenation catalyst, e.g. in the presence of optionally sulphidised palladium on charcoal, or Raney nickel. Further radicals that can be split off by hydrogenolysis are, for example, 2-halo-alkoxycarbonyl radicals, such as the 2,2,2-trichloroethoxy-carbonyl radical or the 2-iodoethoxy- or 2,2,2-tribromoethoxy-carbonyl radical, which can be split off in the usual manner, especially by metallic reduction (so-called nascent hydrogen). Nascent hydrogen can be obtained by the action of metal or of metal alloys, such as amalgams, on agents releasing hydrogen, such as carboxylic acids, alcohols or water, with, in particular, zinc or zinc alloys together with acetic acid being suitable. The hydrogenolysis of 2-halo-alkoxycarbonyl radicals can be performed also by use of chromium(II)-compounds, such as chromium(II)-chloride or chromium(II)-acetate. A radical that can be split off by reduction can also be an aryl sulphonyl group, such as the toluenesulphonyl group, which can be split off in the usual manner by reduction with nascent hydrogen, e.g., by means of an alkali metal, such as lithium or sodium, in liquid ammonia, particularly from a nitrogen atom. In carrying out the reduction, it must be ensured that other reducible groups are not attacked. In the case of the previously described reaction with catalytically activated hydrogen using an unsulphidised hydrogenation catalyst, the procedure is to be carried out, in particular, at low temperature, e.g. between -50° and $+50^\circ\text{C}$, preferably at between 0 and 25°C .

Radicals Z_1 and/or Z_2 and/or Z_3 that can be split off by pyrolysis are, for

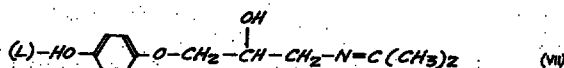
example, optionally substituted, particularly however unsubstituted, carbamoyl groups. Suitable substituents are, e.g., lower alkyl or aryl-lower-alkyl, such as methyl or benzyl, or also aryl, such as phenyl. The pyrolysis is performed in the usual manner, with allowance being made for other thermally sensitive groups. Radicals Z_1 and/or Z_2 and/or Z_3 that can be split off by fermentation are, for example, optionally substituted, particularly however unsubstituted, carbamoyl groups. Suitable substituents are, e.g., lower alkyl or aryl-lower-alkyl, such as methyl or benzyl, also aryl, such as phenyl. The fermentation is performed in the usual manner, e.g. by means of enzyme urease or soya bean extracts, or glucosidase, at about 20°C or at slightly elevated temperature.

In addition, the new compound can be obtained using a procedure whereby in a compound derived from the new compound, in which derived compound the nitrogen atom is bound to one of its substituents by a double bond, the —C=N— double bond is reduced.

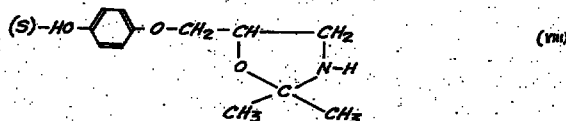
Thus, a schiff base of formula VI



or of formula VII



or a ring tautomer, corresponding to formula VII, of formula VIII



whereby compounds of formulae VII and VIII can also be present together, can be reduced.

This reduction is performed in the usual manner, for example, with a di-light metal-hydride, such as sodium borohydride or lithium aluminium hydride, or with a hydride, such as borane, or formic acid. It is advantageous to use mild reducing agents such as, in particular, alkali metal borohydrides, e.g. sodium borohydride or, preferably, sodium cyanoborohydride, and to operate under mild conditions, e.g. at normal or moderately elevated temperature, and in an inert solvent, such as alkanol, e.g. in ethanol or methanol, or ether, e.g. in diethyl ether, tetrahydrofuran or dioxane, or in water.

Depending on the process conditions and starting materials, the final material is obtained in the free form, or in the form, likewise included in the invention, of its acid addition salts. It is thus possible to obtain, for example, basic, neutral or mixed salts, optionally also hemi-, mono-, sesqui- or polyhydrates thereof. The acid addition salts of the new compound can be converted, in a manner known per se, into the free compound, e.g. with basic agents, such as alkalis or ion exchangers. On the other hand, the resulting free base can form salts with organic or inorganic acids. For the preparation of acid addition salts, there are used, in particular, those acids which are suitable for the obtainment of therapeutically applicable salts. Such acids are, for example: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acids, nitric acid, fumaric acid, aliphatic alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, such as formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, pyruvic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, pamoic, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, halobenzenesulphonic, toluenesulphonic, cyclohexylaminosulphonic or sulphanilic acid.

These or other salts of the new compound, such as picrate, can also serve for purification of the free base obtained, in that the free base is converted into its salt, this is separated, and the base is then liberated from the salt. In consequence of the close relationship between the new compound in the free form and in the form of its salts, it is to be taken, in the foregoing and in the following, that by the

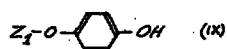
term 'free compound' are meant, where the case applies and with the appropriate modifications, also the corresponding salts.

The invention relates also to those modifications of the process whereby a reaction constituent is optionally present in the form of its salts.

Thus, a compound of formula II wherein X_1 represents hydroxy, and Y_1 stands for $-\text{NH}_2$, can be reacted in a suitable manner with acetone in the presence of a suitable reducing agent, such as one of the above-mentioned. As intermediate, there is obtained a compound of formula VII of VIII, which is then reduced according to the invention.

The starting materials are known or, if they are new, can be obtained by methods known per se.

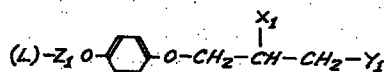
Starting materials of formula II wherein X_1 represents hydroxy, and Y_1 stands for a reactive esterified hydroxy group, or Y_1 together with X_1 forms an epoxy group, can be obtained by, for example, a process in which a compound of formula IX



wherein Z_1 has the above meanings and can be split off by solvolysis, reduction, pyrolysis or fermentation, is reacted with a compound of formula X

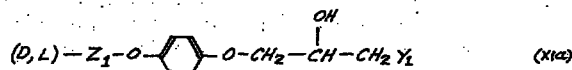


wherein X_1 and Y_1 have the above meanings and preferably together stand for epoxy, and A is a reactive esterified hydroxy group, e.g. the above-mentioned hydroxy group, to give a compound of formula XI

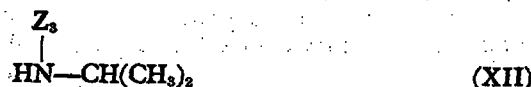


and the group Z_1 is subsequently again split off in the intended manner.

Compounds of formula IV wherein Z_1 stands for a group that can be split off, Z_2 represents hydrogen and Z_3 stands for hydrogen or for a group that can be split off, can be obtained by, for example, a process in which a compound of formula XIa

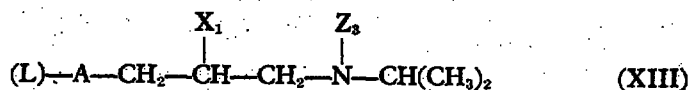


wherein Z_1 has the above meaning and Y is a reactive esterified hydroxy group, is reacted in the usual manner with a compound of formula XII



wherein Z_3 has the above-given meanings or stands for hydrogen; and the L-form is then split off from the racemate, e.g. by one of the aforementioned methods.

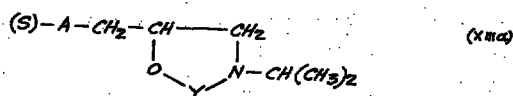
Compounds of formula IV wherein Z_1 stands for a group that can be split off, Z_2 represents hydrogen, and Z_3 stands for hydrogen or for a group that can be split off, can be obtained also by reacting in the usual manner a compound of formula XIII



wherein A is reactive esterified hydroxy, and X_1 is hydroxy, or A and X_1 together are epoxy, or, if Z_3 is hydrogen, A together with the hydrogen atom of the amino group can also be a direct bond with a compound of formula IX.

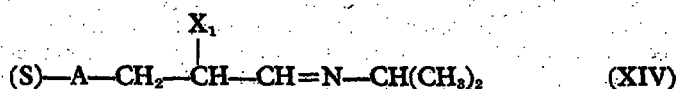
Starting materials of formula V wherein Z_1 and Y have the given meanings can be obtained, for example, by reacting in the usual manner a compound of formula IX with a compound of formula XIIIa

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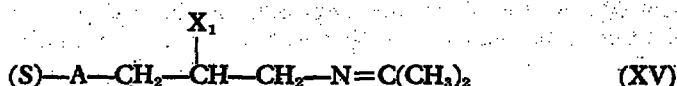


wherein Y has the given meanings, and A stands for a reactive esterified hydroxy group, e.g. for the above-mentioned one.

Compounds of formula VI and VII can be produced by, for example, a process in which a compound of formula IX wherein Z₁ is preferably a group that can be split off by solvolysis, pyrolysis or fermentation, and has the corresponding above-given meanings, is reacted, in the usual manner, with a compound of formula XIV



or with a compound of formula XV



wherein X₁ represents hydroxy, and A stands for a reactive esterified hydroxy group, e.g. for the above-given one, or wherein A and X₁ together form an epoxy group; and subsequently the group Z₁ that can be split off by solvolysis, pyrolysis or fermentation is split off, e.g., in the above-described manner.

The new compound can be used as a pharmaceutically active substance, e.g., in the form of pharmaceutical preparations which contain the new compound, or its salts, in admixture with a pharmaceutical, organic or inorganic, solid or liquid carrier material that is suitable, for example, for enteral, e.g. oral, administration or for parenteral administration. For the formation of this carrier material, suitable substances are ones which do not react with the new compound, such as water, gelatine, lactose, starch, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gum, polyalkylene glycols, Vaseline (Registered Trade Mark), cholesterol or other known carriers for pharmaceutically active substances. The pharmaceutical preparations can be in the form of, for example, tablets, dragées, capsules, suppositories, ointments or creams, or they can be in liquid form as solutions (e.g. as elixir or syrup), suspensions or emulsions. They are optionally sterilised and/or contain auxiliaries, such as preservatives, stabilisers, wetting or emulsifying agents, salts for regulation of the osmotic pressure, or buffers. They may also contain other therapeutically valuable substances. These preparations, which can also be used in veterinary medicine, are manufactured by the customary methods. The daily dose for a warm-blooded animal of about 75 kg body weight is approx. 10—100 mg per os, preferably approx. 20—40 mg per os.

The following examples illustrate the invention without however limiting the scope thereof. The temperature values are given in degrees Centigrade.

Example 1

4.5 g of (+)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane is dissolved in 30 ml of methanol, and a solution of 8.1 g of (+)-di-O,O'-p-toluoyl-D-tartaric acid in 25 ml of methanol and 25 ml of water is added. The solution is then concentrated at room temperature in a water-jet vacuum until commencement of a slight clouding, and subsequently, to allow crystallisation, left to stand at 0° for 15 hours. The precipitated crystals are filtered off with suction, and subsequently recrystallised twice from methanol/water 1:1 to obtain 3.7 g of (-)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropyl-amino)-propane-(+)-di-O,O'-p-toluoyl-D-hydrogen tartrate, M.P. 134—137°.

For isolation of the free enantiomeric base, the salt is taken up in 2N hydrochloric acid, and extracted by shaking with ethyl acetate. (+)-Di-O,O'-p-toluoyl-D-tartaric acid can be regenerated from this extract. The acid solution is rendered alkaline with concentrated ammonia, saturated with sodium chloride and extracted by shaking with ethyl acetate. The organic phase is washed with brine, dried over sodium sulphate and concentrated in a water-jet vacuum. The residue crystallises from ethyl acetate. There is obtained 1.0 g of pure (-)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane, M.P. 129—130°. [α]_D²⁰: -0.9 ± 0.5° (1% solution in

methanol). The neutral fumarate prepared therefrom crystallises from methanol/ether, M.P. 210—211°, $[\alpha]_D^{20}$: $-21.5 \pm 0.5^\circ$ (1% solution in methanol).

Example 2

6.0 g of the diastereoisomer of 1-[p-(β -D-glucopyranosidyloxy)phenoxy]-3-isopropylamino-2-propanol, M.P. 157—160°/186—187°, is dissolved in 20 ml of 2N sulphuric acid and the solution is heated for 3 hours at 80°. The reaction mixture is then cooled, made alkaline with concentrated ammonia, saturated with sodium chloride and extracted with ethyl acetate. The ethyl acetate extract is dried with sodium sulphate and concentrated in a water-jet vacuum. The residue crystallised from ethyl acetate. There is obtained 2.0 g of (—)-1-(4-hydroxy-phenoxy)-2-hydroxy-3-(isopropyl-amino)-propane, $[\alpha]_D^{20}$: $-0.9 \pm 0.5^\circ$ (C=1.0% g/v in methanol). The neutral fumarate prepared therefrom with fumaric acid crystallises from methanol/ether, M.P. 210—211°, $[\alpha]_D^{20}$: $-21.5 \pm 0.5^\circ$ (C=1.01% g/v in methanol).

The starting material required for this reaction can be produced as follows:

27.2 g (0.1 mole) of hydroquinone- β -gluco-pyranoside and 250 ml of epichlorohydrin are dissolved in 1.0 litre of ethanol; 6.9 g (0.05 mole) of potassium carbonate is added and the whole is refluxed for 6 hours. The resulting precipitate is filtered off with suction, and the filtrate is concentrated in a water-jet vacuum. The residue is dissolved in ethanol and filtered. The filtrate is cooled and ether is added until clouding commences. The precipitated reaction product is filtered off with suction and washed with ether. There is thus obtained 4-(2,3-epoxy-propoxy)-phenyl- β -D-glucopyranoside as a mixture of the two possible diastereomers.

25 g of this diastereomer mixture is dissolved in 300 ml of methanol, and the solution is refluxed with 18.5 g of isopropylamine for 6 hours. The reaction mixture is subsequently completely concentrated by evaporation. The residue is dissolved in 35 ml of water, and 11.6 g of cyclohexylsulphamic acid dissolved in acetone is added. Acetone is added to this solution until clouding commences. The reaction products begins to precipitate in crystalline form. To allow completion of crystallisation, the whole is left to stand at 0°C for 15 hours. The precipitated crystals are filtered off with suction and recrystallised from acetone/water. They yield the diastereomer that is not required for the further operation.

The mother liquors occurring during the crystallisation process are combined, and concentrated in a water-jet vacuum to a syrup, which is dissolved in 50 ml of water. This solution is filtered through a column having 200 ml of Amberlite IRA-400® (strongly basic ion exchanger having trimethylammonium groups [particle size 0.38—0.45 mm]). The column is washed with water until the liberated base is completely eluted. The combined aqueous eluates are completely concentrated in a water-jet vacuum, and recrystallised three times from methanol/isopropanol. There is obtained the second diastereomer of 1-[p-(β -D-glucopyranosidyloxy)-phenoxy]-3-isopropyl-amino-2-propanol, M.P. 157—160°/186—189°.

Example 3

Tablets containing 20 mg of active substance are produced, in the normal manner, with the following composition:

Composition

(—)-1-(4-hydroxyphenoxy)-2-hydroxy-3-isopropylamino)propane	10 mg	
wheat starch	60 mg	
lactose	50 mg	
colloidal silicic acid	5 mg	
talcum	9 mg	
magnesium stearate	1 mg	
	135 mg	

Preparation

(—)-1-(4-Hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane is mixed with a portion of the wheat starch, with lactose and colloidal silicic acid, and the mixture is put through a sieve. A further portion of the wheat starch is made into a paste with the 5-fold amount of water on a water bath, and the powder mixture is kneaded with the paste until a slightly plastic mixture is formed.

The plastic mixture is pressed through a sieve of approx. 3 mm mesh size; it is dried and the resulting dry granulate is again put through a sieve. The remaining

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wheat starch and the talcum and magnesium stearate are then mixed in and the mixture is pressed to obtain tablets each weighing 135 mg and having a cross-groove.

Example 4

5 a) A solution of 1.6 g of 1-isopropylamino-2S-hydroxy-3-(4-benzyloxy-phenoxy)-propane-hydrochloride in 160 ml of ethanol is hydrogenated with 0.2 g of 5% palladium on charcoal under normal pressure. After absorption of the calculated amount of hydrogen, the catalyst is filtered off, and the solution is concentrated by evaporation to dryness. The residue is dissolved in 45.6 ml of 0.1N sodium hydroxide solution, and the solution is extracted with ethyl acetate. After drying by means of magnesium sulphate, the organic phase is concentrated by evaporation, and the residue is recrystallised from ethyl acetate to obtain 1-isopropylamino-2S-hydroxy-3-(4-hydroxy-phenoxy)-propane, M.P. 127—128°; $[\alpha]_D^{20} = -1^\circ \pm 1^\circ$; $[\alpha]_{H_2}^{20} = 2^\circ \pm 1^\circ$ (methanol, $c=0.940$).

10 9.1 ml of a 4% solution of fumaric acid in methanol is added to a solution of 0.7 g of the resulting 1-isopropylamino-2S-hydroxy-3-(4-hydroxy-phenoxy)-propane in 5 ml of methanol. Ether is added thereto until clouding commences and the solution is then cooled. The formed crystals are filtered off with suction and dried: they constitute 1-isopropylamino-2S-hydroxy-3-(4-hydroxy-phenoxy)-propane 1/2 fumarate; M.P. 209—211°; $[\alpha]_D^{20} = -23^\circ \pm 1^\circ$; $[\alpha]_{H_2}^{20} = -68^\circ \pm 1^\circ$ (methanol, $c=1.061$).

20 The starting material can be produced as follows:

25 b) a few drops of pyridine are added to a melt, heated to 120°, of 100 g of 5,6-anhydro-1,2-O-isopropylidene- α -D-glucofuranose and 100 g of hydroquinonemono-benzyl ether, with the internal temperature being maintained at below 140° by means of external cooling with lukewarm water. After the exothermic reaction has subsided, the reaction mixture is stirred for a further 30 minutes at 140°, and then cooled to 80°; 500 ml of methanol is added and subsequently water until clouding commences. After several hours' standing at 0°, the precipitated crystals are filtered off with suction and recrystallised from methanol to obtain 1,2-O-isopropylidene-6-O-(4-benzyloxyphenyl)- α -D-glucofuranose; M.P. 99—102°; Rf-value=0.25 on silica gel thin-layer plates in the system methylene chloride: methanol 15:1.

30 c) 500 ml of water is added dropwise, with stirring, to a solution, heated to 70°, of 127.3 g of 1,2-O-isopropylidene-6-O-(4-benzyloxy-phenyl)- α -D-glucofuranose in 800 ml of glacial acetic acid; the whole is further stirred for 14 hours at 70°, and subsequently concentrated in a water-jet vacuum to dryness. The crystalline residue is then recrystallised from 1 litre of glacial acetic acid to obtain 6-O-(4-benzyloxy-phenyl)-D-glucose; M.P. 164—168°; Rf-value=0.61 on silica gel thin-layer plates with methanol; $[\alpha]_D^{20} = -62^\circ \pm 1^\circ$ (methanol, $c=0.985$).

35 d) 64 g of sodium metaperiodate is added portionwise, with stirring and external cooling, in the course of 15 minutes to a suspension of 36.2 g of the resulting 6-O-(4-benzyloxyphenyl)-D-glucose in a mixture of 600 ml of methanol, 10 ml of glacial acetic acid and 60 ml of water, and the whole is stirred at about 25° for 20 hours. The insoluble material is filtered off and the filtrate is concentrated by evaporation to dryness; the residue is taken up in chloroform, this solution is washed with water and dried by means of magnesium sulphate, and the solvent is evaporated off in a water-jet vacuum. The residue is dissolved in 150 ml of methanol, and the solution is added dropwise, during 45 minutes, to a solution, cooled to -5°, of 3.8 g of sodium borohydride in 150 ml of methanol and 40 ml of water. After standing for a further 15 hours at about 25°, the reaction mixture is concentrated by evaporation to dryness; the residue is taken up in chloroform, the solution is washed with ice-cold 2N hydrochloric acid and water and, after drying by means of magnesium sulphate, the solvent is evaporated off in a water-jet vacuum. The residue is recrystallised from chloroform to obtain 1-(4-benzyloxyphenoxy)-2S,3-dihydroxy-propane; M.P. 134—138°; Rf-value=0.32 on silica gel thin-layer plates in the system methylene chloride: methanol 15:1.

40 e) A solution of 5.7 g of p-tosyl chloride in 30 ml of pyridine is added dropwise in the course of 4 hours, with stirring and with the exclusion of moisture, to a solution, cooled to -10°, of 8.2 g of the resulting 1-(4-benzyloxy-phenoxy)-2S,3-dihydroxy-propane in 20 ml of pyridine, and the whole is allowed to stand at about 25° for 16 hours. The reaction mixture is diluted with chloroform and water; the

separated organic phase is washed with ice-cold 2N hydrochloric acid, with water, with a saturated sodium hydrogen carbonate solution and, finally, again with water; it is dried by means of magnesium sulphate and the solvent is removed. The residue is purified by column chromatography on 250 g of silica gel with a mixture of methylene chloride/ethyl acetate 19:1, and the product is recrystallised from an ethyl acetate/petroleum ether mixture to obtain 1-(4-benzyloxy-phenoxy)-2R-hydroxy-3-p-tosyloxy-propane; M.P. 70—74°; Rf-value=0.36 on silica gel thin-layer plates in the system methylenechloride/ethyl acetate 19:1; $[\alpha]_D^{20}=11 \pm 1^\circ$ (chloroform, $c=1.631$).

f) A solution of 3.8 g of 1-(4-benzyloxy-phenoxy)-2R-hydroxy-3-p-tosyloxy-propane in 40 ml of ethanol and 4 ml of isopropylamine is maintained for 30 hours at a temperature of 50°, the subsequently concentrated by evaporation to dryness. The residue is taken up in methylene chloride, the solution is washed with 2N sodium hydroxide solution and then with water, it is dried by means of magnesium sulphate, and the solvent is distilled off to obtain 1-isopropylamino-2S-hydroxy-3-(4-benzyloxyphenoxy)-propane, which is recrystallised from methylene chloride/petroleum ether; M.P. 91—93°.

This compound is dissolved in a small amount of ethanol, and alcoholic hydrochloric acid is added until the pH is 4; ether is then added until cloudiness commences. After cooling, there crystallises out 1-isopropylamino-2S-hydroxy-3-(4-benzyloxyphenoxy)-propane-hydrochloride, which is filtered off with suction and dried; M.P. 161—163°; $[\alpha]_D^{20}=-19 \pm 1^\circ$; $[\alpha]_{H_2}^{20}=-57^\circ \pm 1^\circ$ (methanol: $c=4.903$).

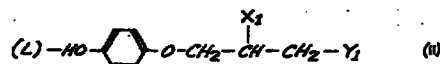
WHAT WE CLAIM IS:—

1. Process for the production of (L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane of formula I



wherein

- the (D,L)-racemate is separated, and the (L)-form is optionally isolated in the form of a salt; or
- a compound of formula II

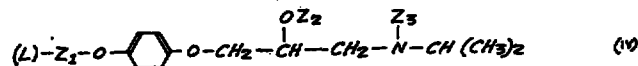


is reacted with a compound of formula III



wherein one of the radicals Y_1 and Y_2 is amino $-NH_2$ and the other is a reactive esterified hydroxy group, and X_1 represents hydroxy, or Y_1 together with X_1 forms an epoxy group, whereby in the latter case the absolute configuration of the epoxide corresponds to the (S)-form and Y_2 is $-NH_2$; or

- in a compound of formula IV



wherein at least one of the radicals Z_1 , Z_2 and Z_3 stands for a group that can be split off, and the remaining radical(s) stand(s) for hydrogen, the group(s) Z_1 and/or Z_2 and/or Z_3 is (are) split off;

- in a compound derived from the new compound, in which derived compound the nitrogen atom is bound to one of its substituents by a double bond, the $-C=N$ -double bond is reduced, and, if desired, the resulting free base is converted into its salts, or resulting salts are converted into the free base.

2. Process according to Claim 1a), wherein the racemate is converted with optically active acids into acid addition salts.

3. Process according to Claim 1a), wherein the acid addition salts are separated into the diastereoisomeric salts, and the optically active (L)-form is split off from the salt.

4. Process according to Claim 1a), wherein the (L)-form is separated from the racemate by fractional crystallisation or by chromatography.

5. Process according to Claim 1b), wherein the reactive esterified hydroxy group

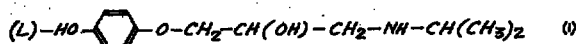
separated organic phase is washed with ice-cold 2N hydrochloric acid, with water, with a saturated sodium hydrogen carbonate solution and, finally, again with water; it is dried by means of magnesium sulphate and the solvent is removed. The residue is purified by column chromatography on 250 g of silica gel with a mixture of methylene chloride/ethyl acetate 19:1, and the product is recrystallised from an ethyl acetate/petroleum ether mixture to obtain 1-(4-benzyloxy-phenoxy)-2R-hydroxy-3-p-tosyloxy-propane; M.P. 70—74°; Rf-value=0.36 on silica gel thin-layer plates in the system methylenechloride/ethyl acetate 19:1; $[\alpha]_D^{20}=11 \pm 1^\circ$ (chloroform, $c=1.631$).

f) A solution of 3.8 g of 1-(4-benzyloxy-phenoxy)-2R-hydroxy-3-p-tosyloxy-propane in 40 ml of ethanol and 4 ml of isopropylamine is maintained for 30 hours at a temperature of 50°, the subsequently concentrated by evaporation to dryness. The residue is taken up in methylene chloride, the solution is washed with 2N sodium hydroxide solution and then with water, it is dried by means of magnesium sulphate, and the solvent is distilled off to obtain 1-isopropylamino-2S-hydroxy-3-(4-benzyloxyphenoxy)-propane, which is recrystallised from methylene chloride/petroleum ether; M.P. 91—93°.

This compound is dissolved in a small amount of ethanol, and alcoholic hydrochloric acid is added until the pH is 4; ether is then added until cloudiness commences. After cooling, there crystallises out 1-isopropylamino-2S-hydroxy-3-(4-benzyloxyphenoxy)-propane-hydrochloride, which is filtered off with suction and dried; M.P. 161—163°; $[\alpha]_D^{20}=-19 \pm 1^\circ$; $[\alpha]_{H_2}^{20}=-57^\circ \pm 1^\circ$ (methanol: $c=4.903$).

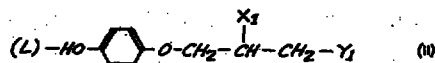
WHAT WE CLAIM IS:—

1. Process for the production of (L)-1-(4-hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane of formula I

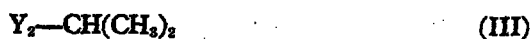


wherein

- a) the (D,L)-racemate is separated, and the (L)-form is optionally isolated in the form of a salt; or
b) a compound of formula II

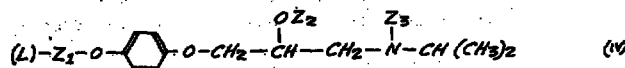


is reacted with a compound of formula III



wherein one of the radicals Y_1 and Y_2 is amino $-NH_2$ and the other is a reactive esterified hydroxy group, and X_1 represents hydroxy, or Y_1 together with X_1 forms an epoxy group, whereby in the latter case the absolute configuration of the epoxide corresponds to the (S)-form and Y_2 is $-NH_2$; or

c) in a compound of formula IV



wherein at least one of the radicals Z_1 , Z_2 and Z_3 stands for a group that can be split off, and the remaining radical(s) stand(s) for hydrogen, the group(s) Z_1 and/or Z_2 and/or Z_3 is (are) split off;

- d) in a compound derived from the new compound, in which derived compound the nitrogen atom is bound to one of its substituents by a double bond, the $-C=N$ -double bond is reduced, and, if desired, the resulting free base is converted into its salts, or resulting salts are converted into the free base.

2. Process according to Claim 1a), wherein the racemate is converted with optically active acids into acid addition salts.

3. Process according to Claim 1a), wherein the acid addition salts are separated into the diastereoisomeric salts, and the optically active (L)-form is split off from the salt.

4. Process according to Claim 1a), wherein the (L)-form is separated from the racemate by fractional crystallisation or by chromatography.

5. Process according to Claim 1b), wherein the reactive esterified hydroxy group



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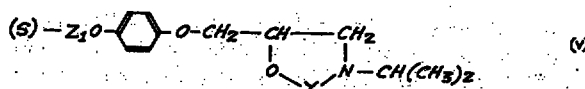
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is a hydroxy group esterified with a hydrohalic acid, sulphuric acid or a sulphonic acid.

6. Process according to Claim 1c), wherein a group that can be split off is a group that can be split off by solvolysis, reduction, pyrolysis or fermentation.

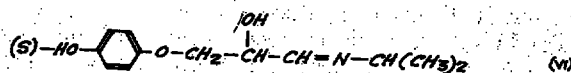
7. Process according to Claim 1c) and 6, wherein a group that can be split off by solvolysis is a group that can be split off by hydrolysis, alcoholysis or acidolysis.

8. Process according to one of Claims 1c), 6 or 7, wherein the compound having radicals that can be split off by hydrolysis is a compound of formula V



wherein Z_1 represents hydrogen or a group that can be split off by hydrolysis, and Y stands for the carbonyl or thiocarbonyl radical, or for a bivalent radical Y_2 of an aldehyde or ketone of the formula $Y_2=O$.

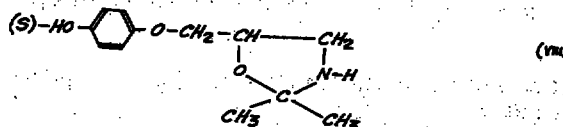
9. Process according to Claim 1d), wherein a Schiff base of formula VI



or of formula VII



or a ring tautomer, corresponding to formula VII, of formula VIII



whereby compounds of formulae VII and VIII can also be present together, is reduced.

10. Process according to one of Claims 1—9, whereby a reaction constituent is optionally used in the form of its salts.

11. Process wherein a compound of formula II wherein X_1 represents hydroxy, and Y_1 stands for $-NH_2$, is reduced with acetone, in the presence of a reducing agent, to the compound of formula I.

12. Process according to one of Claims 1—11, wherein the compound of formula I is obtained in the free form.

13. Process according to one of Claims 1—11, wherein the compound of formula I is obtained in the form of a salt.

14. Process according to one of Claims 1—11 and 13, wherein the compound of formula I is obtained in the form of a therapeutically applicable salt.

15. (L)-1-(4-Hydroxyphenoxy)-2-hydroxy-3-(isopropylamino)-propane.

16. The compound of Claim 15 in the form of a salt.

17. The compound of claim 15 in the form of a therapeutically applicable salt.

18. Pharmaceutical preparations containing a compound claimed in Claim 15 or 17, together with a therapeutically applicable carrier material.

ABEL & IMRAY
Chartered Patent Agents
Northumberland House
303/306 High Holborn
London WC1V 7LH

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