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PATENT SPECIFICATION

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Inventors: FRANZ TROXLER and ALBERT HOFMANN

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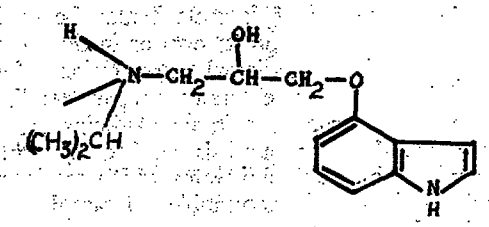
COMPLETE SPECIFICATION

Improvements in or relating to Indole Derivative and method for its production

We, SANDOZ LTD., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate, 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 relates to a new indole derivative and the production thereof. It is divided from our Application No. 1700/66 Serial No. 1138968.

The present invention provides 4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - indole of formula I,

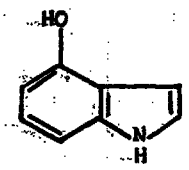


I

and acid addition salts thereof.

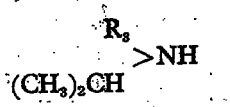
The compound of formula I contains an asymmetric carbon atom, and may therefore exist in optically active forms or as a racemate. In the present specification, however, it is to be understood that any reference to the compound of formula I is intended to embrace only the racemate thereof.

The present invention further provides a process for the production of the compound of formula I and acid addition salts thereof, characterized in that the hydroxy-indole of formula II,



II

in the form of an alkali metal salt, is reacted with epichlorohydrin, the resulting reaction product is heated in the presence of an acid binding agent with an amine of formula III,



III

in which R_3 signifies a hydrogen atom or a benzyl radical, any benzyl radical present in the resulting condensation product is split off by hydrogenolysis and, when an acid addition salt is required, the free base is reacted with an inorganic or organic acid. It will be appreciated that the epichlorohydrin used for the preparation of the compound of formula I is used in the form of its racemate.

One specific method of effecting the process of the invention is as follows:

The hydroxy-indole derivative of formula II is used in the form of an alkali metal salt, preferably the sodium salt; for this purpose it is added to an equimolar amount of aqueous alkali metal hydroxide solution or is reacted in an inert organic solvent, e.g. benzene and toluene, with an equimolar amount of an alkali metal alcoholate, alkali metal amide or alkali metal hydride. 1 to 5 equivalents of epichloro-

[*Price 4s. 6d.*]

hydrin are subsequently added and the mixture is stirred at room temperature for several hours. As the epichlorohydrin molecule has two reactive positions, one usually obtains a mixture of two materials (present in unequal amounts) by this reaction step. As both these materials give rise to only one end product when the next reaction step is effected, it is not necessary to separate the mixture before working up further. Thus the crude mixture resulting by the epichlorohydrin reaction is heated to the boil at reflux for one to several days with an amine of formula III in the presence of an acid binding agent, e.g. a tertiary organic base (for example, pyridine and triethylamine), an inorganic base (for example, potassium carbonate) or, preferably an excess of the amine of formula III. The one of the two epichlorohydrin reaction products present in larger quantity usually reacts at a temperature of 50—60°C, whereas the other one only reacts above that temperature range. When the primary amine of formula III, wherein R_3 signifies a hydrogen atom is used, the required end product is obtained directly, but due to the relatively low boiling point of this amine it is usually necessary to raise the boiling temperature of the mixture to a temperature range which is suitable for the reaction (50—100°C) by the addition of a diluent having a higher boiling point, e.g. toluene, or to effect the reaction in a pressure vessel. However, when the secondary amine of formula III wherein R_3 signifies a benzyl radical is used, which is more suitable for the reaction due to its higher boiling point, the compound of formula I may readily be obtained from the resulting product by splitting off the benzyl radical hydrogenolytically, e.g. by shaking with palladium and hydrogen in an inert solvent.

The compound of formula I may be isolated and purified in the form of the free base or in the form of a salt by methods known *per se*. It is a colourless, crystalline compound, which is difficulty soluble in water and readily soluble in organic solvents. With Keller's reagent (glacial acetic acid containing iron - III - chloride and concentrated sulphuric acid) and van Urk's reagent (*p* - dimethylamino - benzaldehyde and dilute sulphuric acid) it gives characteristic colour reactions.

As pointed out above, the present invention also includes the acid addition salts of the compound of formula I; examples of acids for acid addition salt formation are: hydrochloric, hydrobromic, sulphuric, fumaric, maleic, tartaric, benzoic, methanesulphonic, ethanesulphonic and *p*-toluenesulphonic acid.

In tests effected with animals the compound of formula I exhibits interesting pharmacodynamic properties, especially a pronounced bradycardiac effect of long duration and some blood pressure lowering effect. It inhibits the tachycardia produced by adrenalin and isoprenalin and, particularly, has an inhibiting effect on the circulatory effects of isoprenalin [1 - (3,4 - dihydroxy - phenyl) - 2 - isopropylamino - ethanol] and therefore a blocking effect on the β-receptors of the adrenergic nervous system. The compound has an exceptionally high such blocking effect on β-receptors.

The compound of formula I is therefore indicated for use in therapy, especially in the prophylaxis or treatment of heart diseases, particularly cardiac arrhythmia and angina pectoris. The compound is preferably administered in the form of its water-soluble, physiologically acceptable salts. An indicated suitable daily average dose of the compound of formula I is 1—50 mg.

The compound of formula I may be used as a pharmaceutical on its own or in the form of appropriate medicinal preparations for administration, e.g. enterally or parenterally. In order to produce suitable medicinal preparations the compound is worked up with organic or inorganic adjuvants which are inert and physiologically acceptable. Examples of such adjuvants are:

for tablets and dragées	:	lactose, starch, talc and stearic acid;
for injectable solutions	:	water, alcohols, glycerin and vegetable oils;
for suppositories	:	natural or hardened oils and waxes

The preparations may furthermore contain suitable preserving, stabilizing and wetting agents, solubilizers, sweetening and colouring substances and flavourings.

The present invention also provides pharmaceutical compositions containing in addition to a physiologically acceptable carrier, the compound I and/or a physiologically acceptable acid addition salt thereof.

The hydroxy-indole (II) used as starting material is known.

In the following non-limative Examples all

temperatures are indicated in degrees Centigrade; the melting and boiling points are uncorrected.

EXAMPLE I:

4 - (2 - *hydroxy* - 3 - *isopropylamino* - *propoxy*) - *indole.*

7.3 g of 4 - hydroxy - indole and subsequently 4.5 ml of epichlorohydrin are added whilst stirring in an atmosphere of nitrogen to a solution of 2.25 g of sodium hydroxide in 50 ml of water. Stirring is effected at room temperature for a further 24 hours, the reaction mixture is extracted four times with methylene chloride and the combined organic layers which have been dried over magnesium sulphate are evaporated at reduced pressure. The oily residue is taken up in 50 ml of toluene and 50 ml of isopropylamine and heated at reflux at a bath temperature of 70° for 2½ days. Evaporation to dryness is effected at reduced pressure, the residue is shaken thrice between ethyl acetate and a N tartaric acid solution and a 5N sodium hydroxide solution is then added to the combined tartaric acid phases until an alkaline reaction is obtained. The resulting precipitate is filtered, washed with water and recrystallized from ethanol. Melting point 171—173° (needles).

Keller's colour reaction (0.2 mg)	:	olive green
Van Urk's colour reaction (1 mg)	:	before exposure to light lilac, afterwards dark lilac-violet.

EXAMPLE 2

Example of a medicinal preparation : tablets

	for every tablet
4-(2-hydroxy-3-isopropylamino-propoxy)-indole (compound of Example 1)	0.010 g
Magnesium stearate	0.001 g
Polyvinyl-pyrrolidone	0.004 g
Talcum	0.005 g
Maize starch	0.010 g
Lactose	0.128 g
Dimethyl-silicone oil	0.0005 g
Polyethylene glycol 6000	0.0015 g
	0.160 g

The active compound is mixed in dry state with the magnesium stearate, polyvinyl-pyrrolidone, talcum, maize starch and lactose. The resulting mixture is moistened with an aqueous suspension of dimethyl-silicone oil and polyethylene glycol, the mass is kneaded, granulated and the dried and crushed granulate is pressed into tablets. 100 g of the tabletting mass theoretically yield 625 tablets each weighing 0.160 g and containing 10 mg of active compound.

WHAT WE CLAIM IS:—

1. Racemic 4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - indole.

2. Acid addition salts of racemic 4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - indole.

3. A process for the production of the racemic indole derivative claimed in Claim 1, and its acid addition salts, characterized in that 4-hydroxy indole in the form of an alkali metal salt, is reacted with epichlorohydrin, the resulting reaction product is heated in the presence of an acid binding agent with an amine of formula III,

$$(CH_3)_2CH \diagup \!\!\!> NH \qquad \text{III}$$

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3. A process for the production of the racemic indole derivative claimed in Claim 1, and its acid addition salts, characterized in that 4-hydroxy indole in the form of an alkali metal salt, is reacted with epichlorohydrin, the resulting reaction product is heated in the presence of an acid binding agent with an amine of formula III,



III

* C L M S *

in which R_3 signifies a hydrogen atom or a benzyl radical, any benzyl radical present in the resulting condensation product is split off by hydrogenolysis and, when an acid addition salt is required, the free base is reacted with an inorganic or organic acid.

4. A process for the production of the racemic compound claimed in Claim 1 and its acid addition salts substantially as herein described with reference to Example 1.

5. The racemic compound claimed in Claim 1 and its acid addition salts whenever produced by the process claimed in Claim 3 or 4.

6. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, the racemic compound claimed in Claim 1 and/or a physiologically acceptable acid addition salt thereof.

7. Compositions according to Claim 6, in which the amount of active ingredients present is suitable for the daily administration of from 1 to 50 mg.

8. Compositions according to Claim 6 substantially as hereinbefore described.

For the Applicants:—
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