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PATENT SPECIFICATION

(11) 1 496 491

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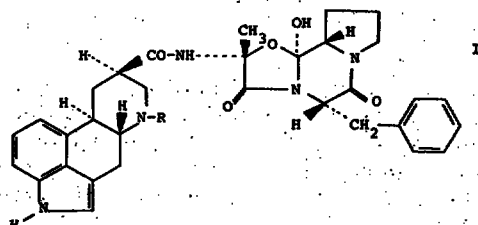
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(54) DIHYDROERGOPEPTINE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, CH-4002 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 new heterocyclic compounds.

In accordance with the invention there are provided new compounds of formula I,

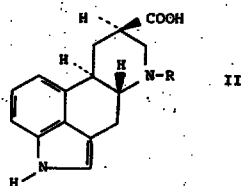


wherein R is hydrogen or alkyl of 2 to 6 carbon atoms.

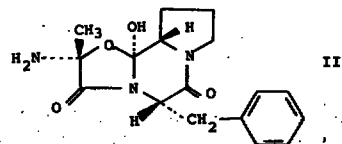
The preferred compounds of formula I wherein R is alkyl of 2 to 6 carbon atoms, are those wherein R contains 2 to 4, especially 2 or 3 carbon atoms, or wherein R is branched, especially in an α position to the nitrogen atom to which R is bound.

R especially signifies isopropyl.

Further, in accordance with the invention a compound of formula I may be obtained by a process comprising condensing a reactive functional derivative of an acid of formula II,



wherein R is as defined above, with the compound of formula III



in the form of a salt, in an inert organic solvent or solvent mixture and in the presence of an acid binding agent.

The compounds of formula I are peptide ergot alkaloids. The reaction of the invention is a condensation reaction for amides. The process of the invention may be effected in a manner analogous to known methods for the production of structurally similar peptide alkaloids.

The condensation is conveniently effected at a temperature between -30 and $+20^{\circ}\text{C}$.

1.2 to 2.4 mols of a reactive derivative of an acid of formula II are conveniently used for every mol of the compound of formula III in salt form.

An example of a suitable reactive derivative of an acid of formula II is the product resulting from the reaction of an acid of formula II with dimethyl formamide or dimethyl acetamide, and thionyl chloride, phosgene or oxalyl chloride.

Examples of suitable inert solvents for the reaction are: chlorinated aliphatic hydrocarbons, such as chloroform or methylenè chloride, dimethyl formamide, or acetonitrile.

Tertiary organic bases, e.g. triethylamine, preferably pyridine, are conveniently used as condensation agents.

It is also possible to use other reactive derivatives of an acid of formula II for the reaction, e.g. the acid chloride hydrochloride, the acid azide, or mixed anhydrides of an acid of formula II with sulphuric or trifluoroacetic acid. However, 6-nor-9,10-dihydrolysergic acid is preferably activated with dimethyl formamide/oxalyl chloride, forming a suitable reactive functional derivative.

The production of these reactive derivatives of an acid of formula II may be effected



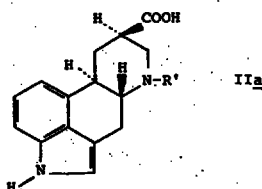
in a manner analogous to known methods, using the corresponding acid.

The working up and isolation are effected in accordance with known methods.

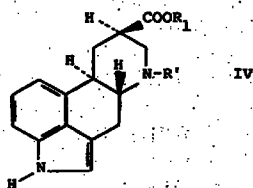
- 5 Acid addition salt forms may be produced from the free base forms in known manner and *vice versa*. Suitable acids for salt formation include methane sulphonic acid and malic acid.

- 10 Of the compounds of formula II 6 - nor - 9,10 - dihydrolysergic acid and 6 - nor - 6-ethyl - 9,10 - dihydrolysergic acid are known [Helv. chim. Acta 53, 2197 f (1970)].

The new compounds of formula IIa,



wherein R' is alkyl of 3 to 6 carbon atoms, are obtained by hydrolyzing a compound of formula IV,



- 20 wherein R' is as defined above, and COOR₁ is an ester radical.

R₁ may, for example, signify lower alkyl of 1 to 4 carbon atoms, e.g. methyl or ethyl.

- 25 The compounds of the formulae IIa and IV are described and claimed in our copending Application No. 23690/77 (Serial No. 1,496,492).

- 30 The compounds of formula IIa are valuable intermediates for the production of pharmacodynamically active 6 - nor - 6 - R' - ergolines wherein R' is as defined above, for example of 6 - nor - 6 - R' - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine compounds wherein R' is as defined above.

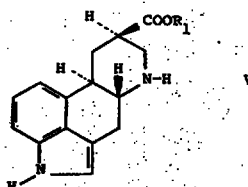
- 35 The hydrolysis of compounds of formula IV may be effected in a manner analogous to known methods for the hydrolysis of lysergic acid esters.

- 40 The hydrolysis is conveniently effected under alkaline conditions, for example by treating a solution of a compound of formula IV in a water-miscible organic solvent or solvent mixture with an alkali metal hydroxide, e.g. caustic soda solution.

- 45 A suitable solvent is, for example, an ether such as dioxane or tetrahydrofuran, or an alkanol such as methanol, and a suitable solvent mixture is, for example, methanol/methylene chloride.

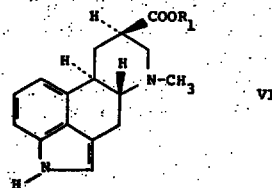
The reaction is effected under mild conditions. When the reaction is effected at room temperature, it has a duration of approximately 24 hours.

The compounds of formula IV are obtained by alkylation of a compound of formula V,



wherein COOR₁ is as defined above.

The alkylation may be effected in a manner analogous to known methods, e.g. as described in Helv. chim. Acta 53, 2197 f (1970). This literature also indicates or describes suitable demethylation methods for the production of 6 - nor - lysergic acid esters. The compounds of formula V are obtained in analogous manner by demethylation of a compound of formula VI,

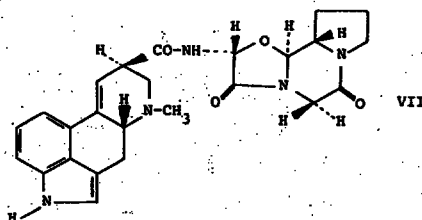


wherein COOR₁ is as defined above.

Insofar as the production of the starting materials is not described, these are known or may be produced in accordance with known processes or in a manner analogous to known processes.

6 - Nor - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine is a valuable starting material for the production of 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine derivatives, e.g. of 6 - nor - 6 - alkyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine compounds such as dihydroergotamine. The latter compounds are obtained by alkylation of the corresponding 6 - nor compounds, e.g. as described for the alkylation of compounds of formula V.

The name of the compounds of formula I is derived from the basic structure of formula VII,



which is named ergopeptine for purposes of simplification.

In the following non-limitative Examples all temperatures are indicated in degrees centigrade. In the following examples "c" is in grams per litre unless otherwise stated.

EXAMPLE 1.

6 - nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine

8.6 cc (100 millimols) of oxalyl chloride dissolved in 20 cc of acetonitrile are added dropwise at -10 to -15° within 10 minutes to a solution of 300 cc of dimethyl formamide and 150 cc of acetonitrile, and stirring is effected for a further 10 minutes. 30 g (100 millimols) of anhydrous 6 - nor - 6 - isopropyl - 9,10 - dihydrolysergic acid are subsequently sprinkled in at -20°, and stirring is effected at -10° for 30 minutes. After cooling to -20°, 200 cc of pyridine and 29.4 g (80 millimols) of a compound of formula III in hydrochloride salt form are added, and stirring is effected at 0° for 2 hours. Working up is effected by adding 100 cc of a buffer solution pH=4 and dividing the reaction mixture between methylene chloride and a 2 N caustic soda solution. The organic phases are washed twice with water, dried over sodium

sulphate and evaporated to dryness on a rotary evaporator. After drying in a high vacuum the resulting crude base is dissolved in approximately 150 cc of ethanol and the solution is seeded. The pure crystalline title compound has an M.P. of 225° (decomp.).

Production of the methane sulphonate:

17 g of pure 6 - nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine are dissolved in 1 liter of acetone, and 2.67 g of methanesulphonic acid are added. Concentration to approximately $\frac{1}{4}$ of the original volume leads to crystallization.

Filtration and washing with acetone yield a pure methane sulphonate having an M.P. of 206-208° (decomp.), $[\alpha]_D^{20} = -23.5^\circ$ (c=0.5 in methanol).

In analogous manner the hydrogen malate salt form is obtained, M.P. 202° (dec.) $[\alpha]_D^{20} = -24^\circ$ (c=0.5 in CH₃OH).

The following compounds of formula I are obtained in a manner analogous to that described in Example 1 by using the corresponding starting materials of formula II and of formula III in salt form:

Example	Compound of formula I			From the compound of formula II having M.P.
	R	M.P.	$[\alpha]_D^{20}$	
2	isobutyl	175-176° (decomp.)	-44.9° (c = 0.862 in methylene chloride)	234-235° (dec.)
3	ethyl	208° (decomp.)	-29.9° (c = 0.473 in dimethyl sulphoxide)	305° (dec.)
4	n-propyl	194° (decomp.)	-23.3° (c = 0.476 in dimethyl sulphoxide)	213-214° (dec.)
5	H	184°	-12.3° (c = 0.881 in methanol)	341-345° (dec.)

EXAMPLE 6.

6 - nor - 6 - isopropyl - 9,10 - dihydrolysergic acid

34.6 g (0.111 mols) of 6 - nor - 6 - isopropyl - 9,10 - dihydrolysergic acid methyl ester are dissolved in 600 cc of methanol and 100 cc of methylene chloride, and 100 cc of a 2 N caustic soda solution are added. After stirring over night at room temperature the organic solvents are removed on a rotary evaporator, and the residue is diluted with 1 liter of water. The pH of the solution is adjusted to 5 with glacial acetic acid, whereby the acid is obtained as jelly-like lump. Heating to 80° gives a clear solution, from which the acid

crystallizes upon cooling. Drying in a high vacuum at 130° leads to the anhydrous title compound having an M.P. of 290° (decomp.), $[\alpha]_D^{20} = -101^\circ$ (c=0.6 in methanol).

The compounds of formula II characterized in the above Table are obtained in a manner analogous to Example 6 by hydrolysis of the corresponding ester.

EXAMPLE 7.

6 - nor - 6 - isopropyl - 9,10 - dihydrolysergic acid methyl ester

40 g (0.148 mols) of 6 - nor - 9,10 - dihydrolysergic acid methyl ester are dissolved

in 400 cc of dimethyl formamide, 61 g of anhydrous potassium carbonate and 139 cc (1.48 mols) of isopropyl bromide are added, and heating is effected to 80° with stirring for 48 hours. After working up and purification the title compound crystallizes from ethanol in the form of colourless crystals having an M.P. of 194°, $[\alpha]_D^{20} = -80.2^\circ$ ($c = 0.582$ in methanol).

The compounds of formula I exhibit pharmacological activity. In particular, they exhibit venoconstrictor activity as indicated in standard tests with animals, for example, by a pressoric effect of long duration in the spinalized cat accompanied by a rise in blood pressure.

The compounds are therefore indicated for use as venotonic agents. For this use an indicated daily dose is from 1.5 to 15 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.4 to 7.5 mg, or in sustained release form.

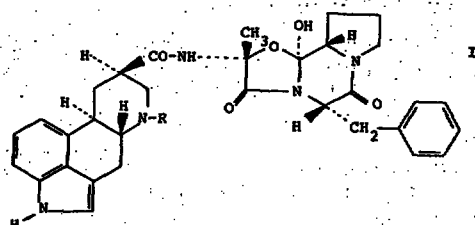
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

In one compound R is hydrogen. In another group of compounds R is alkyl of 2 to 6 carbon atoms.

6 - Nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine has been found to be especially interesting as well as the corresponding 6 - nor - 6 - ethyl and 6 - nor - 6 - propyl compound.

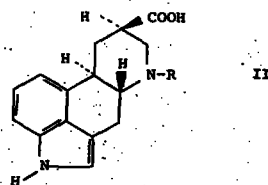
WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,

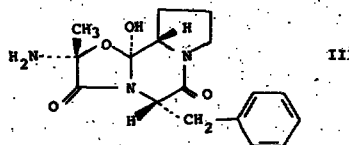


wherein R is hydrogen or alkyl of 2 to 6 carbon atoms, comprising condensing a reactive functional de-

rivative of an acid of formula II,



wherein R is as defined above, with the compound of formula III



in the form of a salt, in an inert organic solvent or solvent mixture and in the presence of an acid binding agent.

2. A process for the production of a compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to any one of the Examples 1 to 5.

3. A compound of formula I as defined in claim 1, whenever produced by a process according to claim 1 or 2.

4. A compound of formula I, as defined in claim 1.

5. The compound of claim 4 which is 6-nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine.

6. The compound of claim 4 wherein R is iso-butyl.

7. The compound of claim 4 wherein R is ethyl.

8. The compound of claim 4 wherein R is n-propyl.

9. The compound of claim 4 wherein R is H.

10. The compound of claim 4 wherein R is alkyl of 2 to 6 carbon atoms.

11. A compound according to any one of claims 3 to 10 in free base form.

12. A compound according to any one of claims 3 to 10 in acid addition salt form.

13. A pharmaceutical composition comprising a compound according to any one of claims 3 to 10 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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Agents for the Applicants.

in 400 cc of dimethyl formamide, 61 g of anhydrous potassium carbonate and 139 cc (1.48 mols) of isopropyl bromide are added, and heating is effected to 80° with stirring for 48 hours. After working up and purification the title compound crystallizes from ethanol in the form of colourless crystals having an M.P. of 194°, $[\alpha]_D^{20} = -80.2^\circ$ ($c = 0.582$ in methanol).

The compounds of formula I exhibit pharmacological activity. In particular, they exhibit vasoconstrictor activity as indicated in standard tests with animals, for example, by a pressoric effect of long duration in the spinalized cat accompanied by a rise in blood pressure.

The compounds are therefore indicated for use as venotonic agents. For this use an indicated daily dose is from 1.5 to 15 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.4 to 7.5 mg, or in sustained release form.

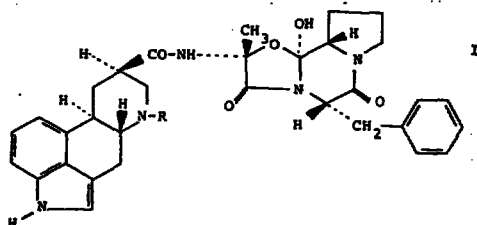
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

In one compound R is hydrogen. In another group of compounds R is alkyl of 2 to 6 carbon atoms.

6 - Nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine has been found to be especially interesting as well as the corresponding 6 - nor - 6 - ethyl and 6 - nor - 6 - propyl compound.

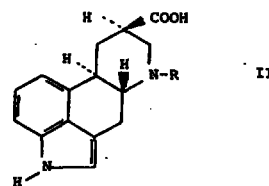
WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,

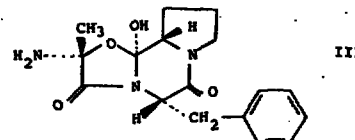


wherein R is hydrogen or alkyl of 2 to 6 carbon atoms, comprising condensing a reactive functional de-

rivative of an acid of formula II,



wherein R is as defined above, with the compound of formula III



in the form of a salt, in an inert organic solvent or solvent mixture and in the presence of an acid binding agent.

2. A process for the production of a compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to any one of the Examples 1 to 5.

3. A compound of formula I as defined in claim 1, whenever produced by a process according to claim 1 or 2.

4. A compound of formula I, as defined in claim 1.

5. The compound of claim 4 which is 6-nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl - ergopeptine.

6. The compound of claim 4 wherein R is iso-butyl.

7. The compound of claim 4 wherein R is ethyl.

8. The compound of claim 4 wherein R is n-propyl.

9. The compound of claim 4 wherein R is H.

10. The compound of claim 4 wherein R is alkyl of 2 to 6 carbon atoms.

11. A compound according to any one of claims 3 to 10 in free base form.

12. A compound according to any one of claims 3 to 10 in acid addition salt form.

13. A pharmaceutical composition comprising a compound according to any one of claims 3 to 10 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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