

1067.827



PATENT SPECIFICATION

1067.827

NO DRAWINGS

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No. 41448/63.

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Patent of Addition to No. 1,011,112 dated May 7, 1962.)

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Int. Cl.:—C 07 d 99/02

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949 are ALBERT HOFMANN, Oberwilerstrasse 11, Bottmingen, Switzerland, ALBERT FREY c/o Ciba Ltd., Basle, Switzerland, HANS OTT, c/o Sandoz Inc., Route 10, Hanover, New Jersey, United States of America, all Swiss Citizens.

COMPLETE SPECIFICATION

Improvements in or relating to Ergostine, Ergostinine and derivatives thereof

We, SANDOZ LTD., a Swiss Body Corporate, of Basle 13, 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:—

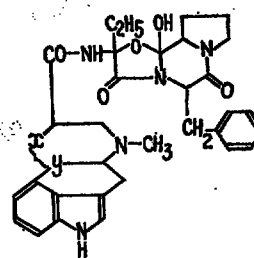
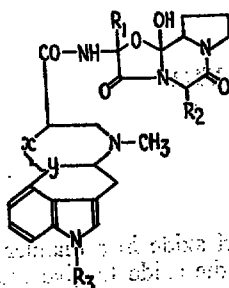
This invention relates to ergot alkaloids and their production and is an improvement in or modification of the invention of our Application No. 17399/62.

In the latter Application, we have described and claimed a process for the production of lysergic acid and dihydrolysergic acid derivatives of the general formula:

$-\text{CH}=\text{C}$ or $-\text{CH}_2-\text{CH}$, and their acid addition salts.

It has now been found that a small group of new compounds within the scope of general formula I have surprisingly greater pharmacodynamic activity, particularly as spasmolytics, than the generality of such compounds.

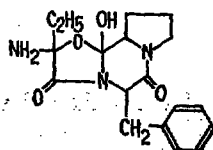
The new compounds are those of the formula:



in which each of R_1 and R_2 signifies a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms inclusive, R_2 signifies a hydrogen atom, an alkyl radical containing from 1 to 3 carbon atoms inclusive or the benzyl radical and $x y$ signifies the radical

II.
in which $x y$ is as hereinbefore defined, and their acid addition salts. There are two stereoisomeric bases of formula II in which $x y$ is $-\text{CH}=\text{C}$ and these two compounds are called herein ergostine and ergostinine. Similarly the base in which $x y$ is $-\text{CH}_2-\text{CH}$ is called 9:10-dihydroergostine.

The present invention also provides a process for the manufacture of the new alkaloids of formula II which comprises reacting (A) lysergic acid chloride hydrochloride or 9:10-dihydrolysergic acid chloride hydrochloride with (B) a salt of 2-amino-2-ethyl-5-benzyl-10b-hydroxy-3:6-dioxo-octahydro-oxazolo[3:2-a]pyrrolo[2:1-c]-pyrazine of the formula:



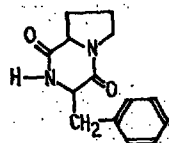
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in the presence of an acid acceptor and, when an acid addition salt is required, salifying with an organic or inorganic acid. According to a preferred procedure the two starting

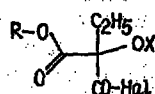
materials are suspended in chloroform or another solvent, and the suspension is mixed with a solution of pyridine or another tertiary amine.

After about 2 hours' reaction the reaction mixture is diluted with an approximately equal amount of chloroform, and then washed with saturated aqueous sodium carbonate solution and finally repeatedly with water. These washings are once more extracted with an organic solvent, the combined organic phases are dried and evaporated under vacuum, and the residue is chromatographically separated into its constituent fractions.

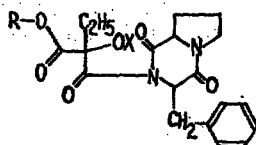
The 2-amino-2-ethyl-5-benzyl-10b-hydroxy-3:6-dioxo-octahydro-oxazolo[3:2-a]pyrrolo[2:1-c]pyrazine used as starting material is new and is advantageously prepared by the following synthetic route, which is described and claimed in our Application No. 47328/66 (1067828), divided out of this Application:



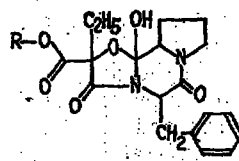
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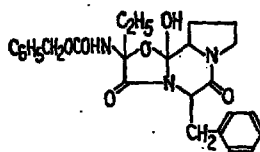
V



VI



VII



VIII

1:4-dioxo-3-benzyl-octahydro-pyrrolo[1:2-a]pyrazine of the formula IV is acylated with a malonic ester derivative of the formula V (in which R represents an alkyl group containing 1 to 5 carbon atoms, X is benzyl, and Hal represents chlorine, bromine or iodine), whereupon the benzyl group X of the resulting compound of the formula VI is eliminated by hydrogenation and the ester of the general formula VII, which results from a spontaneous cyclisation, is then converted into a salt of 2-amino-2-ethyl-5-benzyl-10b-hydroxy-3:6-dioxo-octahydro-oxazolo[3:2-a]pyrrolo[2:1-c]-pyrazine by saponification, formation of the

acid halide and azide in a manner known *per se*, heating of the azide to give the isocyanate which is then reacted with benzyl alcohol to give the benzyl urethane, and hydrogenation of the urethane. [By "in manner known *per se*" as used in this specification is meant any one of the methods heretofore used or described in the chemical literature for converting a carboxylic acid ester into an acid azide by saponification, formation of the acid halide and then the acid azide.] These reactions are described in greater detail in our aforesaid Divisional Application.

The new alkaloid of the general formula I named ergostine is distinguished from ergota-

mine by a substantially different pharmacodynamic activity spectrum, for example by a 10 times greater spasmolytic effect.

The invention includes within its scope pharmaceutical compositions comprising in association with an inert, compatible and pharmaceutically acceptable carrier, one or more compounds of formula II.

The following Examples illustrate the invention. The melting points shown are corrected.

EXAMPLE 1

Ergostine and ergostinine

1 g. of 2-amino-2-ethyl-5-benzyl-10b-hydroxy-3:6-dioxo-octahydro-oxazolo[3:2-a]pyrrolo[2:1-c]pyrazine hydrochloride (isomer A) (prepared as described in our aforesaid Application No. 47328/66) (Serial No. 1067828) and 1 g. of lysergic acid chloride hydrochloride are suspended in 50 cc. of a 3:1-mixture of chloroform and tertiary butanol; a solution of 11 cc. of pyridine is stirred in with cooling, the whole is stirred for 30 minutes, the cooling bath is removed and then the batch is stirred for another 90 minutes at room temperature. The dark brown solution is diluted with 40 cc. of saturated sodium carbonate solution and 40 cc. of chloroform and stirred for 15 minutes. For working up, the batch is diluted with another 60 cc. of chloroform and 40 cc. of water, vigorously agitated, and the two phases are separated. The aqueous phase is extracted another four times with chloroform, and the chloroform solutions are washed once with water, dried with sodium sulphate, and the solvent is expelled from them. The brown crude product, which still contains a small amount of pyridine, is mixed with benzene, suctioned off and then dried in a high vacuum. This crude product is chromatographed on 35 times its own weight of silica gel Merck.

Ergostinine is flushed off the column into the filtrate with a mixture of methylene chloride containing 0.5 to 1% methanol. The combined eluates are evaporated and the residue is recrystallised from acetone; it forms colourless needles melting at 215–216°C. with decomposition.

Optical rotation $[\alpha]_D^{20}$:

+430° (c = 1.15, in pyridine)

+367° (c = 1.0, in chloroform)

Keller's colour reaction: blue, turning green after 2–3 minutes.

Ergostine is eluted from the column with methylene chloride + 2% methanol and purified by recrystallisation from aqueous acetone; it forms handsome prisms melting at 211–212°C. with decomposition.

Optical rotation $[\alpha]_D^{20}$:

–35° (c = 0.7, in pyridine)

–168° (c = 1.6, in chloroform).

Keller's colour reaction: blue, turning green after 15–20 seconds.

Neutral tartrate: melting at 188–191°C. with decomposition.

Acid maleate: melting at 191–192°C. with decomposition.

EXAMPLE 2

9:10-Dihydro-ergostine

10 g. of 2-amino-2-ethyl-5-benzyl-10b-hydroxy-3:6-dioxo-octahydro-oxazolo[3:2-a]pyrrolo[2:1-c]pyrazine hydrochloride (isomer A) and 10 g. of 9:10-dihydro-lysergic acid chloride hydrochloride are suspended in 300 cc. of methylene chloride, and a solution of 16 g. of pyridine in 300 cc. of methylene chloride is vigorously stirred in at 0°C. After 15 minutes at room temperature the solvent is evaporated under vacuum, the residue is taken up in ethyl acetate and extracted by agitation with 2% aqueous tartaric acid solution. The acid aqueous extract is made alkaline with sodium bicarbonate and agitated with ethyl acetate. The ethyl acetate extract is dried with sodium sulphate and evaporated, and the residue is taken up with 300 cc. of hot acetone. 9:10-Dihydro-ergostine crystallises from this solvent in needles which are purified by recrystallisation from 40 times their own weight of hot methanol; they melt at 224–226°C. with decomposition.

Optical rotation $[\alpha]_D^{20}$:

–59° (c = 1.8, in pyridine)

–30° (c = 0.8, in chloroform).

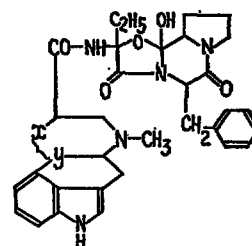
Keller's colour reaction: violet blue; permanent.

Neutral tartrate: Crystallises from methanol on dilution with water in massive prisms melting at 201–203°C. with decomposition.

Acid maleate: Crystallises from methanol in prisms melting at 203–205°C. with decomposition.

WHAT WE CLAIM IS:—

1. The compounds of the formula:



in which x y signifies the radical $-\text{CH}=\text{C}-$ or $-\text{CH}_2-\text{CH}-$ and their acid addition salts.

2. Ergostine and its acid addition salts.
3. Ergostinine and its acid addition salts.



mine by a substantially different pharmacodynamic activity spectrum, for example by a 10 times greater spasmolytic effect.

- 5 The invention includes within its scope pharmaceutical compositions comprising in association with an inert, compatible and pharmaceutically acceptable carrier, one or more compounds of formula II.

- 10 The following Examples illustrate the invention. The melting points shown are corrected.

EXAMPLE 1

Ergostine and ergostinine

- 1 g. of 2 - amino - 2 - ethyl - 5 - benzyl-
15 10b - hydroxy - 3:6 - dioxo - octahydro-oxazolo[3:2 - a]pyrrolo[2:1 - c]pyrazine hydrochloride (isomer A) (prepared as described in our aforesaid Application No. 47328/66) (Serial No. 1067828) and 1 g. of
20 lysergic acid chloride hydrochloride are suspended in 50 cc. of a 3:1-mixture of chloroform and tertiary butanol; a solution of 11 cc. of pyridine is stirred in with cooling, the whole is stirred for 30 minutes, the cooling
25 bath is removed and then the batch is stirred for another 90 minutes at room temperature. The dark brown solution is diluted with 40 cc. of saturated sodium carbonate solution and 40 cc. of chloroform and stirred
30 for 15 minutes. For working up, the batch is diluted with another 60 cc. of chloroform and 40 cc. of water, vigorously agitated, and the two phases are separated. The aqueous phase is extracted another four times with
35 chloroform, and the chloroform solutions are washed once with water, dried with sodium sulphate, and the solvent is expelled from them. The brown crude product, which still contains a small amount of pyridine, is mixed
40 with benzene, suctioned off and then dried in a high vacuum. This crude product is chromatographed on 35 times its own weight of silica gel Merck.

- 45 *Ergostine* is flushed off the column into the filtrate with a mixture of methylene chloride containing 0.5 to 1% methanol. The combined eluates are evaporated and the residue is recrystallised from acetone; it forms colourless needles melting at 215—216°C. with decomposition.

Optical rotation $[\alpha]_D^{20}$:

- +430° (c = 1.15, in pyridine)
+367° (c = 1.0, in chloroform)

- 55 Keller's colour reaction: blue, turning green after 2—3 minutes.

- Ergostine* is eluted from the column with methylene chloride + 2% methanol and purified by recrystallisation from aqueous acetone; it forms handsome prisms melting at 211—
60 212°C. with decomposition.

Optical rotation $[\alpha]_D^{20}$:

- 35° (c = 0.7, in pyridine)
—168° (c = 1.6, in chloroform).

Keller's colour reaction: blue, turning green after 15—20 seconds. 65

Neutral tartrate: melting at 188—191°C. with decomposition.

Acid maleate: melting at 191—192°C. with decomposition.

EXAMPLE 2

9:10-Dihydro-ergostine

10 g. of 2 - amino - 2 - ethyl - 5 - benzyl-
10b - hydroxy - 3:6 - dioxo - octahydro-oxazolo[3:2 - a]pyrrolo[2:1 - c]pyrazine hydrochloride (isomer A) and 10 g. of 9:10-dihydro-lysergic acid chloride hydrochloride are suspended in 300 cc. of methylene chloride, and a solution of 16 g. of pyridine in 300 cc. of methylene chloride is vigorously stirred in at 0°C. After 15 minutes at room
75 temperature the solvent is evaporated under vacuum, the residue is taken up in ethyl acetate and extracted by agitation with 2% aqueous tartaric acid solution. The acid aqueous extract is made alkaline with sodium bicarbonate and agitated with ethyl acetate. The ethyl acetate extract is dried with sodium sulphate and evaporated, and the residue is taken up with 300 cc. of hot acetone. 9:10-Dihydro-ergostine crystallises from this solvent in needles which are purified by recrystallisation from 40 times their own weight of hot methanol; they melt at 224—226°C. with decomposition. 90

Optical rotation $[\alpha]_D^{20}$:

- 59° (c = 1.8, in pyridine)
—30° (c = 0.8, in chloroform).

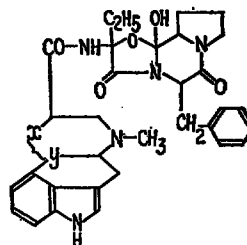
Keller's colour reaction: violet blue; permanent. 95

Neutral tartrate: Crystallises from methanol on dilution with water in massive prisms melting at 201—203°C. with decomposition. 100

Acid maleate: Crystallises from methanol in prisms melting at 203—205°C. with decomposition. 105

WHAT WE CLAIM IS:—

1. The compounds of the formula:



in which x y signifies the radical —CH=C 110
or —CH₂—CH and their acid addition salts.

2. Ergostine and its acid addition salts.
3. Ergostinine and its acid addition salts.

4. 9:10-Dihydro-ergostine and its acid addition salts.
5. Process for the manufacture of a compound as claimed in claim 1 which comprises reacting (A) lysergic acid chloride hydrochloride or 9:10-dihydrolysergic acid chloride hydrochloride with (B) a salt of 2 - amino-2 - ethyl - 5 - benzyl - 10b - hydroxy - 3:6 - dioxo - octahydro - oxazolo - [3:2 - a] - pyrrolo[2:1 - c]pyrazine in the presence of an acid acceptor and, when an acid addition salt is required, salifying with an organic or inorganic acid.
- 15 6. Process according to claim 5 in which the salt (B) is produced in the manner claimed

in our Application No. 47328/66, 1067828).

7. Process according to claim 5 substantially as described in the Examples.

8. A compound as claimed in any of claims 1 to 4 when produced by the process defined in any of claims 5 to 7.

9. Pharmaceutical compositions comprising, in association with an inert, compatible and pharmaceutically acceptable carrier, one or more compounds as claimed in any of claims 1 to 4.

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* C L N S *