

PATENT SPECIFICATION

(11) 1 567 484

1 567 484

- (21) Application No. 53303/76 (22) Filed 21 Dec. 1976
 (31) Convention Application No. 16680/75
 (32) Filed 23 Dec. 1975
 (31) Convention Application No. 6188/76
 (32) Filed 18 May 1976 in
 (33) Switzerland (CH)
 (44) Complete Specification published 14 May 1980
 (51) INT CL³ C07D 457/12 A61K 31/48
 (52) Index at acceptance

C2C 1364 213 247 250 252 25Y 29X 29Y 304 30Y 314 31Y 321
 327 32Y 337 340 34Y 351 354 366 368 37X 385 440 45X
 45Y 511 514 51Y 520 527 577 617 620 627 628 657 65X
 670 678 72Y 740 759 802 80Y AA BC KA ME NF SC

- (72) Inventors PETER STÜTZ
 THEODOR FEHR and
 PAUL STADLER

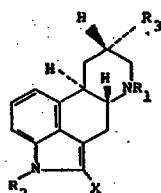


(54) ERGOLINE I DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 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 ergoline derivatives.

The present invention provides compounds of formula I,



wherein:

- X is hydrogen, chlorine or bromine,
 R₁ is methyl or ethyl,
 R₂ is alkyl of 1 to 4 carbon atoms or allyl,
 R₃ is CH₂CN or a group —NR₄R₅,
 wherein R₄ is hydrogen or alkyl of 1 to 4 carbon atoms, and R₅ is alkanoyl of 1 to 5 carbon atoms alkoxy carbonyl of 2 to 5 carbon atoms in the aggregate thereof, or mono-, di- or tri-haloalkoxy carbonyl of 3 to 5 carbon atoms, wherein the alkoxy group is substituted by halogen other than in the α position to the oxygen atom, or R₅ is SO₂R₆, wherein R₆ is alkyl of 1 to 4 carbon atoms, mono-, di- or tri-haloalkyl of 1 to 4 carbon atoms, phenyl, phenyl mono-substituted by halogen or alkoxy of 1 to 4 carbon atoms, pyridyl, or R₆ is a group NR₇R₈, wherein R₇ and R₈ are, independently, hydrogen or alkyl or 1

to 4 carbon atoms, or R₇ and R₈ together form



wherein n is a whole number from 3 to 7, and A is oxygen, sulphur, or nitrogen substituted by alkyl of 1 to 4 carbon atoms or phenyl.

X is preferably hydrogen.

Except where otherwise stated alkyl and alkoxy have preferably 2, especially, 1 carbon atom.

R₁ is preferably methyl.

R₂ is preferably alkyl.

R₃ is preferably the group NR₄R₅.

R₄ is preferably hydrogen.

When R₅ is alkanoyl or alkoxy carbonyl, this preferably contains 1 or 3 carbon atoms.

When R₅ and/or R₆ contains a halogen atom, this is fluorine, chlorine or bromine, and especially chlorine or fluorine. When R₅ and/or R₆ contains more than one halogen substituent, then these substituents are preferably identical.

R₅ is preferably SO₂R₆.

When R₆ is mono-, di- or tri-haloalkyl, this preferably contains 1 to 3 carbon atoms. When R₆ is mono-substituted phenyl, the substituent is preferably halogen and especially chlorine or fluorine.

R₆ is preferably C₁₋₄ alkyl, phenyl, phenyl, mono-substituted by halogen or alkoxy of 1 to 4 carbon atoms, pyridyl or group NR₇R₈.

When R₇ and/or R₈ is alkyl, this contains preferably 1 to 3 carbon atoms, especially 2 or 1 carbon atom. R₇ and R₈ are preferably identical. n is preferably 4 or 5.

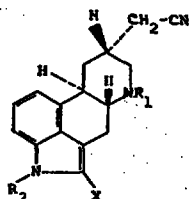
A is preferably oxygen.

A preferred group of compounds includes compounds of formula I, wherein X is

hydrogen. R_1 and R_2 are each methyl and R_3 is NHSO_2R_4 , wherein R_4 is C_{1-4} alkyl, phenyl, phenyl mono-substituted by halogen, pyridyl, di(C_{1-4} alkyl)amino or morpholino.

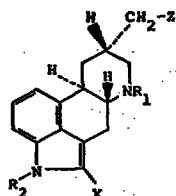
The present invention comprises a process

a) for the production of a compound of formula Ia,



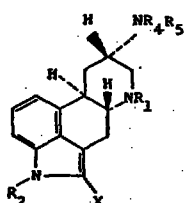
Ia

wherein X, R_1 and R_2 are defined above, replacing the group Z in a compound of formula II,



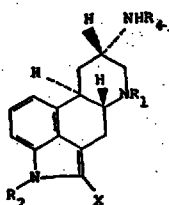
II

wherein Z is a leaving group, and X, R_1 and R_2 are as defined above, by a cyano group, b) for the production of a compound of formula Ib



Ib

wherein X, R_1 , R_2 , R_4 and R_5 are as defined above, reacting a compound of formula III,



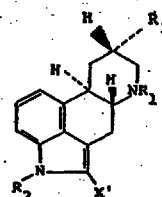
III

wherein X, R_1 , R_2 and R_4 are as defined above, with a reactive functional derivative of a compound of formula



wherein R_5 is as defined above, or

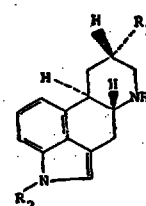
c) for the production of a compound of formula Ic,



Ic

30

wherein X' is chlorine or bromine, and R_1 , R_2 and R_3 are as defined above, introducing a halogen atom into the 2-position of the ergoline nucleus of a compound of formula Id,



Id

35

wherein X' , R_1 , R_2 and R_3 are as defined above.

Process a) may be carried out in conventional manner for a nucleophilic substitution.

Z is preferably chlorine, bromine, or an aliphatic or aromatic sulfonyloxy radical, preferably mesyloxy or p-tosyloxy. As a suitable cyano group donor may be used an alkali metal cyanide such as sodium or potassium cyanide.

Suitable reaction temperatures may be from 50° to 100°C .

Process b) may be effected in conventional manner for a N-acylation. When R_5 is formyl, the reactive functional derivative is preferably the mixed acid anhydride of formic acid and acetic acid, otherwise the corresponding acid halide, e.g. the acid chloride or bromide may be used. Alternatively, when R_5 is alkanoyl of 2 to 5 carbon atoms, the corresponding symmetrical acid anhydride may be used. The reaction is conveniently effected in a solvent, e.g. methylene chloride or dioxane. When an acid anhydride is used, an excess thereof may be used as solvent.

Suitable reaction temperatures lie between -10°C and room temperature. When R_5 is formyl and when the mixed acid anhydride mentioned above is used, a slightly higher temperature, e.g. 40° to 60°C may be used.

Preferably a tertiary base such as triethylamine, pyridine or 2,6-dimethylpyridine is present.

Process c) may be effected in conventional manner for such halogenation reactions. Suitable halogenation agents include N- X' -succinimide or N- X' -phthalimide, wherein X' is as defined above.

Suitable solvents are dioxane or chloroform. The reaction may be effected at from 10° to 100°C.

Free base forms of the compounds of formula I may be converted into acid addition salt form in conventional manner and vice versa. The hydrochloride is a suitable salt.

Insofar as the preparation of the starting materials is not particularly described, these may be produced in conventional manner or as described in the Examples.

In the following Examples all temperatures are in degrees Centigrade, and are uncorrected.

EXAMPLE 1:

1,6-Dimethyl-8 α -(N,N-dimethylsulfamoyl-amino)ergoline-(I)

2.55 g (10 millimol) of 1,6-dimethyl-8 α -amino-ergoline I are dissolved in 20 ml of 2,6-lutidine and are added dropwise within 10 minutes to a stirred mixture of 3.58 g (25 millimol) of N,N-dimethylsulfamic acid chloride, 40 ml of methylene chloride and 10 ml of 2,6-lutidine. Upon stirring for one hour at room temperature 1.5 ml of N,N-dimethylsulfamic acid chloride are added and stirring is effected for 2 hours at room temperature. Working up is effected by adding 2N ammonia at 0° until basic and extraction is effected with a mixture of 10% methanol in methylene chloride. Upon drying over sodium sulphate, the organic phase is treated with active charcoal and is concentrated by evaporation at the rotary evaporator. The resulting, greenish foam is chromatographed on 150 g of silica gel, whereupon the title compound is eluted with 2% methanol in methylene chloride as yellowish resin. The hydrochloride of the title compound crystallizes from ethanol, M.P. 226°—228° [α]_D²⁰ = -23° (c=0.3 in pyridine).

The 1,6-dimethyl-8 α -amino-ergoline I required as starting compound is obtained by hydrogenation of 1-methyl- $\Delta^{7,8}$ -lysergic acid methyl ester (catalysed by addition of platinum oxide), reaction of the resulting 1-methyl-9,10-dihydro-isolysergic acid I-methyl ester (M.Pt. 150°—151°) with a mixture of hydrazine hydrate and hydrazine dihydrochloride and conversion of the resulting 1-methyl-9,10-dihydro-isolysergic acid I-hydrazide (M.Pt. 208°—211°) according to Curtius.

EXAMPLE 2:

Analogous to Example 1 the following compounds are obtained:—

a) 1,6-dimethyl-8 α -N-ethoxycarbonyl-N-methylamino-ergoline I; M.Pt 228°—230° (hydrochloride); [α]_D²⁰ = -26° (c=0.3 in dimethylformamide).

b) 1,6-dimethyl-8 α -ethoxycarbonylamino-

ergoline I; M.Pt. 300°—301° (hydrochloride) (decomp.); [α]_D²⁰ = +43° (c=0.3 in dimethylformamide). 65

c) 1,6-dimethyl-8 α -(N,N-diethylsulfamoyl-amino)-ergoline I; M.Pt. 199°—201° (methanesulphonate); [α]_D²⁰ = -25° (c=0.3 in dimethylformamide). 70

EXAMPLE 3:

1,6-Dimethyl-2-bromo-8 α -(N,N-dimethyl-sulfamoylamino)-ergoline I

1.5 g of 1,6-dimethyl-8 α -(N,N-dimethylsulfamoyl-amino)-ergoline I are added to 125 ml of dioxane (absolute). 1.2 g of N-bromo-succinimide in 100 ml of dioxane are added dropwise while stirring and the resulting brown solution is stirred for another 2 hours at room temperature. The reaction mixture is concentrated by evaporation, dissolved in methylene chloride, treated with active charcoal and is worked up in the usual way. The residue is dried for 30 minutes in a high vacuum at 60°. The hydrochloride of the title compound (from ethanol) has a M.Pt. of 252°—254° (decomposition). The optical rotation amounts to [α]_D²⁰ = +10° (c=1 in dimethyl formamide). 75 80 85 90

The compounds of formula I exhibit pharmacological activity. In particular, they exhibit prolactin secretion inhibiting activity as indicated in standard tests, e.g. an inhibition of ovum implantation on female rats on the fifth day after insemination on administration s.c. of a dose of from 0.01 to 5 mg/kg animal body weight of the compounds. The test may be carried out as follows:— 95 100

The compound under investigation is administered to female rats 5 days after coitus and shown to be sperm positive according to the vaginal smear test. The rats are sacrificed on day 12 and their uteri are examined by means of the Salewski reaction for proof that the nidation process has been interrupted [Arch. exp. Path. Pharm. 247 367 (1967)]. 105

The compounds are therefore indicated for use as prolactin secretion inhibitors. An indicated daily dose is from 0.5 to 50 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from 0.1 mg to 25 mg of the compound or in sustained release form. 110 115

The compounds of formula I, wherein R₃ is —NHSO₂N(CH₃)₂, especially the Example 1 compound, exhibit particularly interesting activity in this test. 120

The compounds of formula I exhibit central dopaminergic stimulant activity, as indicated by standard tests, for example according to the principles of U. Ungerstedt Acta Physiol. Scand. Suppl. (1971) 367, 69—93, by an induction of contralateral turning in rats lesioned unilaterally in the substantia 125

13

nigra by 6-hydroxydopamine an i.p. administration of from 0.3 to 5 mg/kg animal body weight and by an induction of dose dependent stereotyped sniffing, licking and biting behaviour in the rat according to the following test:—

Rats, 180—222 g, are placed in Perspex [Registered Trade Mark] cylinders of 30 cm diameter on a wire grid floor. After 30 minutes to allow acclimatisation to the cage, the rats are injected with the compound under investigation. The behaviour of the rats is observed for 2 minutes at 30 minute intervals for 2 hours and then at 60 minute intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Naylor and Olley [Euro J. Pharmac. 18, 83—94 (1972)].

The score and criteria are as follows:—
1. Intermittent sniffing
2. Persistent sniffing, occasional licking
3. Licking, occasional biting
4. Intense and persistent biting.

In this test the compounds are administered i.p. at from 1 to 40 mg/kg animal body weight.

The compounds are therefore indicated for use as anti-Parkinson agents. An indicated daily dose is from 10 to 200 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from 2.5 to 100 mg or in sustained release form.

The compounds of formula I exhibit additionally anti-depressant activity, as indicated in standard tests, e.g. by an inhibition of the tetrabenazine-induced catalepsy in rats on i.p. administration of from 1 to 50 mg/kg of the compounds.

The compounds are therefore further indicated for use as anti-depressant agents. An indicated daily dose is from 5 to 20 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from 1 mg to 10 mg, or in sustained release form.

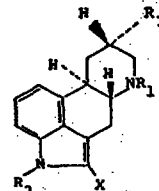
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition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

In a group of compounds R_1 is methyl; R_2 is C_{1-4} alkyl and R_3 is $-NHSO_2NR_4R_5$,

wherein R_4 and R_5 are, independently, alkyl of 1 to 4 carbon atoms.

WHAT WE CLAIM IS:—

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



I

70

wherein:

X is hydrogen, chlorine or bromine,

R_1 is methyl or ethyl,

R_2 is alkyl of 1 to 4 carbon atoms or allyl,

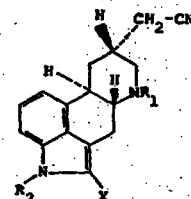
R_3 is CH_2CN or a group $-NR_4R_5$,

wherein R_4 is hydrogen or alkyl of 1 to 4 carbon atoms, and R_5 is alkanoyl of 1 to 5 carbon atoms, alkoxycarbonyl of 2 to 5 carbon atoms in the aggregate thereof, or mono-, di- or tri-

haloalkoxycarbonyl of 3 to 5 carbon atoms, wherein the alkoxy group is substituted by halogen other than in the α position to the oxygen atom, or R_5 is SO_2R_6 , wherein R_6 is alkyl of 1 to 4 carbon atoms, mono-, di- or tri-

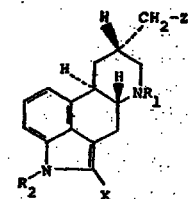
haloalkyl of 1 to 4 carbon atoms, phenyl, phenyl mono-substituted by halogen or alkoxy of 1 to 4 carbon atoms, or pyridyl, or R_6 is a group NR_7R_8 , wherein R_7 and R_8 are, independently, hydrogen or alkyl of 1 to 4 carbon atoms, or R_7 and R_8 together form $-(CH_2)_n-$ or $-(CH_2)_2-A-(CH_2)_2-$, wherein n is a whole number from 3 to 7, and A is oxygen, sulphur, or nitrogen substituted by alkyl of 1 to 4 carbon atoms, or phenyl, which comprises

a) for the producing of a compound of formula Ia,



Ia

wherein X, R_1 and R_2 are defined above, replacing the group Z in a compound of formula II,



II

105

nigra by 6-hydroxydopamine an i.p. administration of from 0.3 to 5 mg/kg animal body weight and by an induction of dose dependent stereotyped sniffing, licking and biting behaviour in the rat according to the following test:—

Rats, 180—222 g, are placed in Perspex [Registered Trade Mark] cylinders of 30 cm diameter on a wire grid floor. After 30 minutes to allow acclimatisation to the cage, the rats are injected with the compound under investigation. The behaviour of the rats is observed for 2 minutes at 30 minute intervals for 2 hours and then at 60 minute intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Naylor and Olley [Euro J. Pharmac. 18, 83—94 (1972)].

The score and criteria are as follows:—

1. Intermittent sniffing
2. Persistent sniffing, occasional licking
3. Licking, occasional biting
4. Intense and persistent biting.

In this test the compounds are administered i.p. at from 1 to 40 mg/kg animal body weight.

The compounds are therefore indicated for use as anti-Parkinson agents. An indicated daily dose is from 10 to 200 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from 2.5 to 100 mg or in sustained release form.

The compounds of formula I exhibit additionally anti-depressant activity, as indicated in standard tests, e.g. by an inhibition of the tetraabenazine-induced catalepsy in rats on i.p. administration of from 1 to 50 mg/kg of the compounds.

The compounds are therefore further indicated for use as anti-depressant agents. An indicated daily dose is from 5 to 20 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from 1 mg to 10 mg, or in sustained release form.

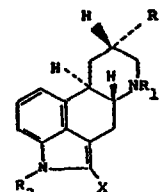
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition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

In a group of compounds R_1 is methyl; R_2 is C_{1-4} alkyl and R_3 is $-NHSO_2NR_4R_5$.

wherein R_1 and R_2 are, independently, alkyl of 1 to 4 carbon atoms.

WHAT WE CLAIM IS:—

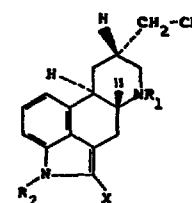
1. A process for the production of a compound of formula I,



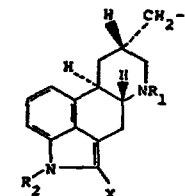
wherein:

- X is hydrogen, chlorine or bromine,
- R_1 is methyl or ethyl,
- R_2 is alkyl of 1 to 4 carbon atoms or allyl,
- R_3 is CH_2CN or a group $-NR_4R_5$, wherein R_4 is hydrogen or alkyl of 1 to 4 carbon atoms, and R_5 is alkanoyl of 1 to 5 carbon atoms, alkoxy carbonyl of 2 to 5 carbon atoms in the aggregate thereof, or mono-, di- or trihaloalkoxy carbonyl of 3 to 5 carbon atoms, wherein the alkoxy group is substituted by halogen other than in the α position to the oxygen atom, or R_5 is SO_2R_6 , wherein R_6 is alkyl of 1 to 4 carbon atoms, mono-, di- or trihaloalkyl of 1 to 4 carbon atoms, phenyl, phenyl mono-substituted by halogen or alkoxy of 1 to 4 carbon atoms, or pyridyl, or R_6 is a group NR_7R_8 , wherein R_7 and R_8 are, independently, hydrogen or alkyl of 1 to 4 carbon atoms, or R_7 and R_8 together form $-(CH_2)_n-$ or $-(CH_2)_2-A-(CH_2)_2-$, wherein n is a whole number from 3 to 7, and A is oxygen, sulphur, or nitrogen substituted by alkyl of 1 to 4 carbon atoms, or phenyl, which comprises

- a) for the producing of a compound of formula Ia,



wherein X, R_1 and R_2 are defined above, replacing the group Z in a compound of formula II,



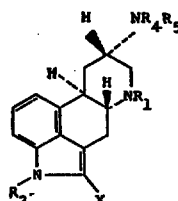


* C L M S *

1,567,484

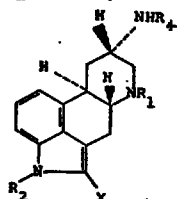
5

wherein Z is a leaving group, and X, R₁ and R₂ are as defined above, by a cyano group, b) for the production of a compound of formula Ib,



Ib

wherein X, R₁, R₂, R₄ and R₅ are as defined above, reacting a compound of formula III,

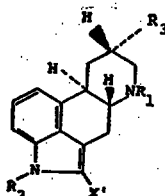


III

wherein X, R₁, R₂ and R₄ are as defined above, with a reactive functional derivative of a compound of formula

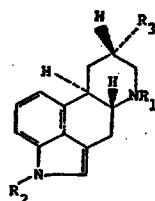


wherein R₅ is as defined above, or c) for the production of a compound of formula Ic,



Ic

wherein X' is chlorine or bromine, and R₁, R₂ and R₃ are as defined above, introducing a halogen atom into the 2-position of the ergoline nucleus of a compound of formula Id,



Id

wherein X', R₁, R₂ and R₃ are as defined above.

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.

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

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

5. A compound of claim 4, wherein X is hydrogen, R₁ and R₂ are both methyl, R₃ is —NHSO₂R₆¹, wherein R₆¹ is C₁₋₄ alkyl, phenyl, phenyl mono-substituted by halogen, pyridyl, di (C₁₋₄ alkyl)amino or 1-morpholino.

6. A compound of Claim 4, wherein R₁ is methyl; R₂ is C₁₋₄ alkyl and R₃ is —NHSO₂NR₇¹R₈¹, wherein R₇¹ and R₈¹ are, independently, alkyl of 1 to 4 carbon atoms.

7. 1,6-Dimethyl-8α-(N,N-dimethylsulfamoylamino)ergoline-(I).

8. 1,6-Dimethyl-8α-N-ethoxycarbonyl-N-methylamino-ergoline I.

9. 1,6-Dimethyl-8α-ethoxycarbonylamino-ergoline I.

10. 1,6-Dimethyl-8α-(N,N-diethylsulfamoylamino)ergoline I.

11. 1,6 - Dimethyl - 2 - bromo - 8α - (N,N - dimethylsulfamoylamino)ergoline I.

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

13. A compound according to any one of claims 3 to 11 in acid addition salt form.

14. A pharmaceutical composition comprising a compound according to any one of claims 3 to 11 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

B.A. YORKE & CO:
Chartered Patent Agents
98, The Centre,
Feltham,
Middlesex TW13 4EP
Agents for the Applicants