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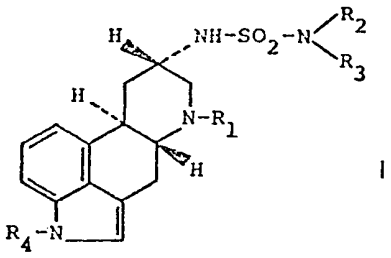
(54) **Ergoline Derivatives, their Production and Pharmaceutical Compositions Containing them**

(57) A compound of formula I



I

wherein
$R_1$ is ethyl or n-propyl,
$R_2$ is hydrogen or alkyl ($C_{1-3}$),
$R_3$ is alkyl ($C_{1-3}$), and
$R_4$ is hydrogen or methyl
in free base form or in pharmaceutically acceptable acid addition salt form is useful as a prolactin secretion inhibitor, anti-parkinson and anti-depressant agent.

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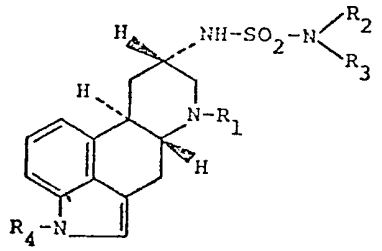
SPECIFICATION

# Ergoline Derivatives, their Production and Pharmaceutical Compositions Containing them

This invention relates to ergoline derivatives, their production and pharmaceutical compositions containing them.

The present invention provides compounds of formula I



I

wherein $R_1$ is ethyl or n-propyl,
$R_2$ is hydrogen or alkyl($C_{1-3}$),
$R_3$ is alkyl($C_{1-3}$), and
$R_4$ is hydrogen or methyl.

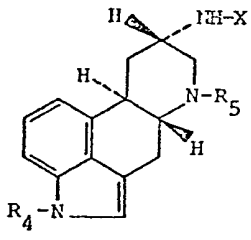
Broad classes of ergolines, having prolactin secretion inhibition and dopaminergic activity e.g. anti-parkinson activity and encompassing the present compounds of formula I wherein $R_4$ is hydrogen, have been published in the literature for example Swiss patent No. 605938. In this Swiss patent it is specifically mentioned that the 6-position of the ergoline nucleus is preferably substituted by methyl or an $\alpha$-branched alkyl radical such as isopropyl. All the characterised examples have a methyl group in the 6-position.

DOS 2656344 discloses a broad class of ergolines having the above-mentioned activities and encompassing the present compounds of formula I wherein $R_1$ is ethyl and $R_4$ is methyl. It is mentioned that the preferred substituent on the 6-position is methyl, and all the characterised examples have the 6-substituent as methyl.

None of the present compounds which have an ethyl or n-propyl substituent in the 6-position of the ergoline nucleus have been, however, specifically disclosed or suggested by the literature, and it has been found that they have a very interesting pharmacological profile, and are particularly well tolerated and potent, e.g. as indicated the pharmacological tests mentioned hereinafter.

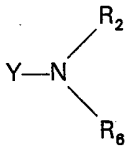
The substituent $R_1$ is preferably n-propyl. Preferably $R_2$ and $R_3$ are identical and preferably they are methyl or ethyl.

The present invention also provides a process for the production of a compound of formula I as claimed in claim 1 which includes the step of condensing a compound of formula II



II

or a precursor thereof with a compound of formula III



III

or a precursor thereof
wherein $R_2$ and $R_4$ are as defined above,
$R_5$ is hydrogen, ethyl or n-propyl,
$R_6$ is hydrogen or alkyl($C_{1-3}$),
and one of X and Y is $SO_2Z$ wherein Z is a leaving group, and the other of X and Y is hydrogen.

The reaction is preferably effected by reacting a compound of formula II wherein X is hydrogen with a compound of formula IV

$$Z—SO_2—NR_2R_6 \qquad IV$$

wherein $R_2$ and $R_6$ and Z are as defined above.

The reaction may be effected in conventional manner for the production of analogous compounds. Z is preferably chlorine or bromine. Suitable solvents include, for example, appropriate chlorinated aliphatic hydrocarbons such as methylene chloride or chloroform or appropriate cyclic or open chain ethers such as dioxane. Suitable reaction temperatures may be between about —10 and about 80°C.

The compound of formula II and/or III may be used in the form of a precursor, e.g. in protected form and then deprotected later. The protecting group may for example be attached to a nitrogen atom and may for example be an amino-protecting group.

Naturally if $R_5$ or $R_6$ is hydrogen, then a subsequent alkylation is necessary to produce a compound of formula I. Besides the alkylation in position 1 or 6 of the ergoline nucleus, the sulfamoyl group may be easily alkylated.

Any desired further conversion, e.g. alkylation, may be effected in conventional manner. The type, amounts of alkylating agents used, and reaction conditions may naturally be chosen, if desired, along with temporary protection of amine groups, to effect alkylation selective in position 1, or 6 or effect mono or dialkylation in the sulfamoyl group.

An alkylation in position 1 or 6 of the ergoline nucleus may be, for example, effected by reaction of the corresponding compound unsubstituted in position 1 or 6 with a compound of formula $CH_3—Z$ or $R_1—Z$ respectively wherein $R_1$ is as defined above and Z is a leaving group, e.g. halogen of atomic number 9 to 53 or an organic sulphonic acid radical e.g. tosyloxy.

The reaction is preferably effected in an inert organic solvent, conveniently at temperatures of between about 10 and about 100°C and suitably in the presence of a base. The alkylation in position 6 may alternatively be effected under reductive conditions, e.g. by catalytic hydrogenation under mild reaction conditions.

Alkylation on the sulfamoyl nitrogen may be effected in conventional manner for alkylation of amines. Naturally it is to be appreciated that when $R_1$ or $R_4$ in the starting material is hydrogen then these positions may be alkylated first.

The reaction is preferably effected with an alkyl halide in acetone, dimethylformamide or a chlorinated hydrocarbon in the presence of a base. If a monoalkylation on the sulfamoylamino nitrogen atom is required (and if desired alkylation in positions 1 or 6 of the ergoline nucleus) the alkyl halide is preferably used in at most equivalent amounts based on the ergoline starting material. If a dialkylation of the sulfamoylamino nitrogen is required then the alkyl halide is preferably used in excess.

The compounds of formula I may be isolated and purified in conventional manner.

Free base forms of the compounds of formula I may be converted into acid addition salt forms in conventional manner and vice versa. Suitable acids for salt formation include for example hydrochloric acid, sulphuric acid, maleic acid, fumaric acid and tartaric acid.

Compounds of formula II wherein X is $SO_2Z$ may be obtained by introducing the group $SO_2Z$ into the corresponding compounds of formula II wherein X is hydrogen. When Z is chlorine this may be effected for example by reacting a compound of formula II wherein X is hydrogen with sulphuryl chloride, if necessary with temporary protection of the nitrogen atom in positions 1 or 6 of the ergoline nucleus when $R_1$ or $R_4$ is hydrogen.

Some of the compounds of formula II wherein X is hydrogen are new, for example, compounds of formula II wherein X is hydrogen, $R_4$ is hydrogen or methyl and $R_5$ is hydrogen and compounds of formula II wherein X is hydrogen, $R_4$ is methyl and $R_5$ is n-propyl. All the compounds of formula II wherein X is hydrogen may be produced in conventional manner from 8$\alpha$-amino-6-methyl-ergoline. Thus the 8$\alpha$-amino group may be protected by e.g. benzyloxycarbonyl. The 6-methyl group can then be replaced by a group $R_1$ and the 1 position may be methylated.

Insofar as the production of any starting material is not particularly described, these are known or may be produced in conventional manner.

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

**Example 1**

**8$\alpha$-(N,N-diethylsulfamoylamino)-6-n-propyl-ergoline**

[alternative nomenclature N,N-diethyl-N'-(6-propylergolin-8$\alpha$-yl)sulfamide]

A solution of 2 ml (ca 26 mM) diethyl-sulfaminic acid chloride in 5 ml chloroform is added dropwise to a refluxing solution of 2.2 g (8.2 mM) 8$\alpha$-amino-6-n-propyl-ergoline in 50 ml chloroform and 5 ml triethylamine. The mixture is refluxed for 12 hours, and then cooled to room temperature. 10 ml of 2N sodium hydroxide are added and the mixture is stirred for 1 hour at room temperature. To work up, extraction is effected three times with methylene chloride/isopropanol (9:1). The combined organic phases are dried with sodium sulphate, filtered and concentrated to yield the title compound.

The hydrochloride salt form is recrystallized from ethanol/methylene chloride (1:1). M.pt. 160—162°; $[\alpha]_D^{20}$=—56° [c=0.4 in ethanol/water (1:1)].

The ergoline starting material may be obtained as follows:—

**a) 8$\alpha$-benzyloxycarbonylamino-6-methylergoline**

10.5 ml (75 mM) carbobenzyloxychloride are added to a suspension of 18 g (74.7 mM) 8$\alpha$-amino-6-methylergoline in 1000 ml chloroform, 150 ml isopropanol and 37 ml 2N (74 mM) sodium hydroxide at room temperature. The mixture is stirred for 2 hours at room temperature. After separation of the organic phase, this is dried, filtered and concentrated. The resultant crude product is filtered through silicagel with methylene chloride/methanol (99:1) giving the heading compound as a foam.

**b) 8$\alpha$-benzyloxycarbonylamino-6-cyanoergoline**

A solution of 29.5 g (79 mM) of 8$\alpha$-benzyloxycarbonylamino-6-methylergoline obtained from step a) and 25 g (236 mM) cyano-bromide in 600 ml chloroform is stirred for 65 hours at room temperature and finally concentrated on a rotary evaporator to give the heading compound which is dried in a high vacuum.

**c) 8$\alpha$-benzyloxycarbonylaminoergoline**

18 g (46.5 mM) of 8$\alpha$-benzyloxy-carbonylamino-6-cyanoergoline obtained from step b) in 100 ml acetic acid are added to a suspension of 40 g zinc in 100 ml acetic acid. 40 ml water are added and the mixture is heated at 100° for 10 hours. To work up, the mixture is filtered through a filtering aid such as Hyflo and concentrated in a rotary evaporator. The residue is partitioned between potassium bicarbonate aqueous solution and methylene chloride/isopropanol (9:1). The organic phase is dried over sodium sulphate, filtered and concentrated to give the heading compound in crude form.

**d) 8$\alpha$-benzyloxycarbonylamino-6-n-propylergoline**

A suspension of 17.5 g (ca 46 mM) of 8$\alpha$-benzyloxycarbonylaminoergoline obtained form step c), 13.5 g potassium carbonate and 6 ml (62 mM) n-propyl iodide in 300 ml dimethylformamide is stirred for 18 hours at room temperature. The mixture is filtered and concentrated in a rotary evaporator. The residue is

treated with methylene chloride and shaken with water. The organic phase is dried over sodium sulphate, filtered and concentrated to give the crude heading compound.

**e) 8α-amino-6-n-propylergoline**

12 g (ca 30 mM) of 8α-benzyloxy-carbonylamino)-6-n-propylergoline obtained from step d) and 1.5 g palladium in charcoal (10% by weight) in 500 ml ethanol are hydrogenated at normal pressure until hydrogen uptake ceases. The mixture is filtered and concentrated. This resultant heading compound is crystallised from methanol.

In analogous manner to that described in Example 1 the following compounds of formula I are obtained by reacting the appropriate compound of formula II and a compound of formula IV, wherein X is H and Y is $ClSO_2$:—

**Example 2**

**6-ethyl-8α-(N,N-dimethyl-sulfamoylamino)ergoline**

Hydrochloride salt: M.pt from 210° decomp.; $[\alpha]_D^{20}$=—70° [c=0.37 in ethanol/water (1:1)].

**Example 3**

**1-methyl-8α-(N,N-dimethylsulfamoylamino)-6-n-propylergoline**

Hydrochloride salt: M.pt. from 220° decomp.; $[\alpha]_D^{20}$=—60° [c=0.445 in ethanol/water (1:1)].

**Example 4**

**6-ethyl-8α-(N,N-diethyl-sulamoylamino)ergoline**

Hydrochloride salt: M.pt. from 180° decomp.; $[\alpha]_D^{20}$=—61° [c=0.45 in ethanol/water (1:1)].

**Example 5**

**8α-(N,N-dimethylsulfamoylamino)-6-n-propylergoline**

Hydrochioride salt: M.pt. from 220° decomp.; $[\alpha]_D^{20}$=—63° [c=0.43 in ethanol/water (1:1)].

**Example 6**

**6-ethyl-8α-(N,N-dimethylsulfamoylamino)-1-methylergoline**

Hydrochloride salt: M.pt. from 230° decomp.; $[\alpha]_D^{20}$=—75° [c=0.44 in ethanol/water (1:1)].

**Example 7**

**8α-(N,N-diethylsulfamoylamino)-1-methyl-6-n-propylergoline**

Hydrochloride salt: M.pt. from 180° decomp.; $[\alpha]_D^{20}$=—31.5° [c=0.96 in pyridine].

**Example 8**

**8α-(N-methylsulfamoylamino)-6-n-propylergoline**

Free base: 103—107°.

The compounds of formula I have not been described in the literature.

The compounds of formula I exhibit pharmacological activity. In particular, they exhibit prolactin secretion inhibition activity as indicated by an inhibition of the implantation of fertilized eggs in the uterus on day 5 after insemination of female rats on administration of from about 0.001 to about 0.1 mg/kg s.c. of the compounds [according to the principles of Experienta *34*, 1330 (1978)].

The compounds are therefore furthermore indicated for use as prolactin secretion inhibition agents, e.g. for the treatment of endocrinological indications associated with prolactin secretion.

An indicated daily dosage is in the range from about 0.1 to about 1 mg conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.003 mg to about 0.5 mg of the compounds, or in sustained release form.

Additionally the compounds of formula I exhibit dopaminergic activity as indicated by an induction of contralateral turning in rats with a unilateral 6-hydroxydopamine-induced degeneration at doses of about 0.05 to about 2 mg/kg i.p. [According to the principles of U.Ungerstedt, Act.physiol. Scand. Suppl. *367*, 69—93, (1971)].

The compounds are therefore additionally indicated for use as anti-parkinson agents.

An indicated daily dosage for this indication is in the range from about 0.5 to about 10 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.15 mg to about 5 mg of the compounds or in sustained release form.

Moreover, the compounds of formula I exhibit anti-depressant activity as indicated in animal tests, e.g. an antagonism of reserpine-induced catalepsy and ptosis is observed at doses of from about 0.01 to about 0.1 mg/kg s.c.

The compounds are therefore furthermore indicated for use as anti-depressant agents.

As indicated daily dosage for this indication is in the range from about 1 to about 10 mg, conveniently given in divided doses 2 to 4 times a day or in unit dosage form containing from about 0.5 mg to about 5 mg of the compounds, or in sustained release form.

The Example 1 compound is the preferred compound and the prolactin secretion inhibition indication is the preferred indication.

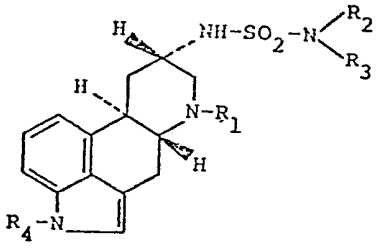
The invention also includes compounds for use in the above-mentioned indications, i.e. prolactin secretion inhibition, Morbus Parkinson and depression.

The compounds may be administered in the form of a pharmaceutically acceptable acid addition salt. Such salt forms have the same order of activity as the free base forms. The present invention accordingly provides 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 n-propyl and $R_4$ is methyl.

**Claims**

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

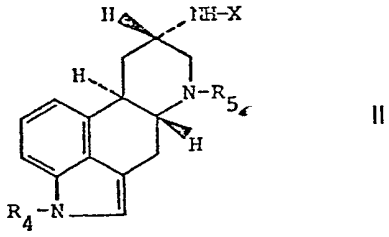


I

wherein

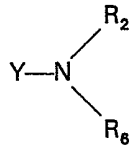
$R_1$ is ethyl or n-propyl,
$R_2$ is hydrogen or alkyl($C_{1-3}$),
$R_3$ is alkyl ($C_{1-3}$), and
$R_4$ is hydrogen or methyl,

which includes the step of condensing a compound of formula II



II

or a precursor thereof with a compound of formula III



III

or a precursor thereof,

wherein $R_2$ and $R_4$ are as defined in claim 1 and
$R_5$ is hydrogen, ethyl or n-propyl,
$R_6$ is hydrogen or alkyl($C_{1-3}$),

and one of X and Y is $SO_2Z$ wherein Z is a leaving group and the other of X and Y is hydrogen.

2. A process as claimed in claim 1 wherein at least one of $R_2$, $R_4$, $R_5$ and $R_6$ is hydrogen and the resultant compound is alkylated to produce a compound of formula I.

3. A process for the production of a compound of claim 1 substantially as hereinbefore described with reference to any one of the Examples.

4. A compound of claim 1 whenever produced by a process of claim 1, 2 or 3.

5. A compound of formula I as defined in claim 1.

6. A compound of claim 5 wherein $R_1$ is n-propyl and $R_4$ is methyl.

7. A compound of claim 5 which is 8$\alpha$-(N,N-diethylsulfamoylamino)-6-n-propylergoline.

8. A compound of claim 5 which is 6-ethyl-8$\alpha$-(N,N-dimethylsulfamoylamino)ergoline.

9. A compound of claim 5 which is 1-methyl-8$\alpha$-(N,N-dimethylsulfamoylamino)-6-n-propylergoline.

10. A compound of claim 5 which is 6-ethyl-8$\alpha$-(N,N-diethylsulfamoylamino)ergoline.

11. A compound of claim 5 which is 8$\alpha$-(N,N-dimethylsulfamoylamino)-6-n-propylergoline.

12. A compound of claim 5 which is 6-ethyl-8$\alpha$-(N,N-dimethylsulfamoylamino)-1-methyl-ergoline.

13. A compound of claim 5 which is 8$\alpha$-(N,N-diethylsulfamoylamino)-1-methyl-6-n-propyl-ergoline.

14. A compound of claim 5 which is 8$\alpha$-(N-methylsulfamoylamino)-6-n-propylergoline.

15. A compound of any one of claims 4 to 14 in free base form.

16. A compound of any one of claims 4 to 14 in acid addition salt form.

17. A compound of claims 4 to 14 in free base form or in pharmaceutically acceptable acid addition salt form for use as a prolactin secretion inhibitor, an anti-parkinson agent or an anti-depressant agent.

18. A pharmaceutical composition which comprises a compound of any one of claims 4 to 14 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

19. A method of inhibiting prolactin secretion, treating Morbus Parkinson or depressions in a subject which comprises administering a therapeutically effective amount of a compound of any one of claims 4 to 14 in free base form or in pharmaceutically acceptable acid addition salt form to a subject in need of such treatment.

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