COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

618290

APPLICATION FOR A STANDARD PATENT

We Sandoz Ltd. of Lichtstrasse 35, CH-4002 Basle, Switzerland

hereby apply for the grant of a Standard Patent for an invention entitled:

"A novel 8α-acylaminoergoline"

which is described in the accompanying complete specification.

This application is made under the provisions of Section 51 of the Patents Act 1952 in respect of Australian Patent No. 583489 in the name of Sandoz Ltd.

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

4 February, 1991

To: THE COMMISSIONER OF PATENTS

Keith Davies

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention

Insert title of invention

entitled: A NOVEL 8α-ACYLAMINOERGOLINE

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

We Jean Kramer and Hans Rudolf Haus, of SANDOZ LTD., 35 Lichtstrasse, CH-4002 Basle, SWITZERLAND

do solemnly and sincerely declare as follows: -

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)

1(b) relates to application made by company; insert name of applicant company.

1. (a) I am / We are ~~the person named in the accompanying declaration~~

or (b) ~~I am~~ authorized by SANDOZ LTD.

the applicant..... for the patent to make this declaration on its / ~~their~~ behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)

2(b) relates to application made by company(s) or person(s) who are not inventor(s), insert full name(s) and address(es) of inventors.

2. (a) ~~I am / We are the person named in the accompanying declaration~~

or (b)

Walter Haefliger, Dorf, CH-6262, Langnau, SWITZERLAND

is / ~~are~~ the actual inventor..... of the invention and the facts upon which the applicant..... is / ~~are~~ entitled to make the application are as follows :-

State manner in which applicant(s) derive title from inventor(s)

The inventor has assigned the invention to the applicant and the right to claim priority from the basic application has been assigned to the applicant by Sandoz-Patent-GmbH.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

~~3. The basic application as defined by Section 141 of the Act~~ was / were made

in on the

by

in on the

by

in on the

by

4 The basic application referred to in paragraph 3 of this Declaration was / were the first application made in a Convention country in respect of the invention the subject ~~of the application~~

Insert place and date of signature

Declared at Basle this 24th day of November 1988

Signature of declarant(s) (no attestation required)

SANDOZ Ltd.

Note Initial all alterations

DAVIES & COLLISON, MELBOURNE and CANBERRA

duly authorized Officer

duly authorized Officer

(12) PATENT ABRIDGMENT (11) Document No. AU-B-25067/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 618290

(54) Title
A NOVEL 8ALPHA-ACYLAMINOERGOLINE

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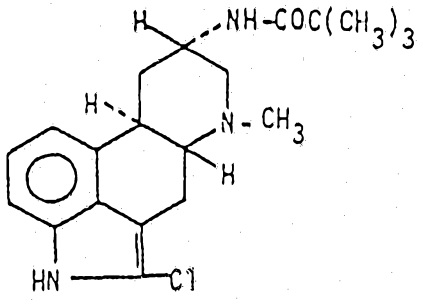
(56) Prior Art Documents
GB 1517971
GB 1567484

(57) The present invention relates to a novel 8α-acylamino-ergoline, processes for its production, pharmaceutical compositions containing it and its use as a pharmaceutical.

CLAIM

1. The compound of formula I



(I)

or acid addition salt thereof.

4. A pharmaceutical composition comprising the compound as defined in claim 1 or pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

C O M M O N W E A L T H O F A U S T R A L I A

PATENTS ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

618290

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name of Applicant: SANDOZ LTD.

Address of Applicant: LICHTSTRASSE 35, CH-4002 BASLE, SWITZERLAND

Actual Inventor(s): Walter Haefliger, Dorf, CH-6262 Langnau, Switzerland

Address for Service: DAVIES & COLLISON, Patent Attorneys, 1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

A NOVEL 8α-ACYLAMINOERGOLINE

The following statement is a full description of this invention, including the best method of performing it known to us. :-

Case 100-6238/III

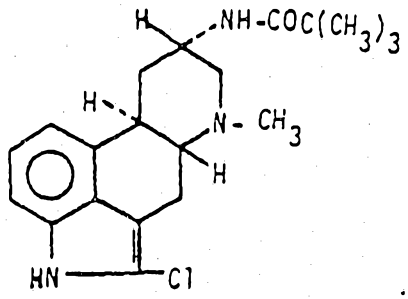
A NOVEL 8α-ACYLAMINOERGOLINE

The present invention relates to a novel 8α-acylamino-ergoline, processes for its production, pharmaceutical compositions containing it and its use as a pharmaceutical.

The 8α-ergolines comprises a major class of compounds possessing varying degrees and type of biological activity and potential therapeutic utility. Thus Australian Patent Specifications 505,314 and 514,288 disclose a wide range of ergoline derivatives which are variously 8α-substituted. Amongst possible 8α-substituents embraced there are included numerous derivatised amino groupings including i.a. acylamino and related residues. The subject compounds are variously described as possessing dopaminergic and prolactin secretion inhibiting activity.

The present invention provides a novel 8α-acylamino-ergoline, which has been found to possess especially interesting or advantageous biological activity or profile.

More particularly the present invention relates to the compound of formula I



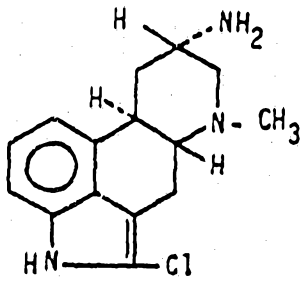
(I)

as well as the acid addition salts thereof.

The compound of formula I falls under the scope of Australian Patent Specification 505 314, but is there not specifically disclosed. The compounds of the Australian Patent Specification possess prolactin secretion inhibiting and dopamine agonist activity. The present claimed compound has neuroleptic activity.

The present invention also provides a process for the production of the compound of formula I and its acid addition salts, which process comprises:

a) reacting the compound of formula II



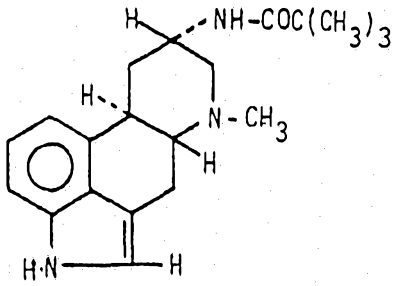
(II)

with the compound of formula III

$$C(CH_3)_3COOH \qquad (III)$$

or a reactive functional derivative thereof, or

b) chlorinating the compound of formula Ia



(Ia)

and recovering the obtained compound of formula I as such or as an acid addition salt thereof.

Process step a) may be carried out in accordance with standard procedures. Suitable reactive functional derivatives of the compound of formula III include e.g. the corresponding acyl halides, in particular chlorides, and imidazolides. Reaction with acylhalides is suitably effected in the presence of a base, such as triethylamine or Hünig-base. Reaction with imidazolides (obtained e.g. by reaction of the compound of formula III with N,N-carbonyldiimidazole) is suitably carried out in an inert solvent such as tetrahydrofuran or ethanol, e.g. at reflux temperature. Where compound of formula III is employed as such, reaction may suitably be effected e.g. in the presence of propanephosphonic acid anhydride.

Process step b) may also be carried out in accordance with known techniques, using standard chlorinating agents such as N-Cl-succinimide or sulphuryl chloride. The reaction is conveniently performed in the presence of an inert diluent or sovent such as methylene chloride or tetrahydrofuran.

The starting material of formula II may be produced analogously to the known compounds and in accordance with known procedures. The starting material for step b) may be prepared in accordance with process step a).

The compound of formula I may be recovered from the initially obtained reaction medium as such (i.e. in free base form) or in acid addition salt form e.g. in the form of their pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable acid addition salts include both such salts with inorganic acids, for example the hydrochloride salts, as well as such salts with organic acids, for example the oxalates and maleates.

The following examples are illustrative of the processes for the production of the subject compound :

EXAMPLE 1:

Preparation of 8α-benzoylamino-6-n-propylergoline

1.4 ml benzoylchloride in 5 ml CH_2Cl_2 are added drop-wise with stirring at 5 - 10 ° C to a suspension of 3.0 g 8α-amino-6-n-propylergoline in 100 ml CH_2Cl_2 and 2.0 ml triethylamine. The obtained reaction mixture is stirred for 15 to 20 hours at 20 ° C and then washed thoroughly 2 x with 25 ml 2N NaOH and H_2O. The organic phase is dried over $MgSO_4$, filtered and evaporated. The residue (pale brown foam) is dissolved in ethanol, and crystallised as the hydrobromide by addition of equivalent amounts of HBr in acetic acid. M.P. on recrystallisation from C_2H_5OH/H_2O (80 : 2) = 290 ° with decomposition.

Analogously is obtained 2-chloro-6-methyl-8α-pivaloylamino-ergoline, m.p. 215-216°C.

EXAMPLE 2:

Preparation of 2-chloro-6-n-propyl-8α-pivaloylamino-ergoline

1 g silica gel are added to 2 g 6-n-propyl-8α-pivaloylamino-ergoline (example 2) in 50 ml methylene chloride, pre-cooled to 0 ° C. 0.503 ml sulfurylchloride are added drop-wise and the reaction mixture stirred for 4 hours. 1N potassium carbonate solution is added, the mixture extracted with methylene chloride, dried over Na_2SO_4 and concentrated. The residue is chromatographed on 50 g silica gel using toluene/ethylacetate (2 : 1) as eluant to yield the title compound. M.P. = 146 - 147 ° C.

Analogously is obtained 2-chloro-6-methyl-8α-pivaloylamino-ergoline, m.p. 215-216 °C.

The compound of formula I and its pharmaceutically acceptable acid addition salts possess pharmacological activity as can be shown in standard animal test methods, and are accordingly indicated for use as pharmaceuticals.

In particular compound for formula I and its pharmaceutically acceptable acid addition salts, possess apomorphine antagonistic activity as demonstrated in the test method described by Jansson et al., Arz. Forsch. 10, 1003, (1960). Thus compound of formula I inhibits apomorphine (10 mg/kg s.c.) induced, stereotyped gnawing over periods of several hours, at dosages of from 0.032 mg/kg s.c..

Apomorphine antagonist activity as demonstrable in the relevant test method described above is also demonstrable of dopamine antagonist activity. Thus compound of formula I may be characterised as having a dual dopamine agonist/antagonist activity profile.

In view of its apomorphine antagonistic activity compound of formula I and its pharmaceutically acceptable acid addition salts are indicated for use as neuroleptic agents, for example for the treatment of schizophrenia.

For the above uses, the dosage required will of course vary depending on e.g. the mode of administration, the particular condition to be treated and the effect desired.

However an indicated daily dosage is in the range of:

1) from about 0.05 to about 5.0 mg for use in PRL secretion inhibition;
2) from about 1 to about 10 mg for use in LH secretion inhibition; and
3) from about 1 to about 40 mg, for neuroleptic use,

of compound of formula I, conveniently administered in divided doses of 2 to 4x/day in unit dosage form or in sustained release form. Suitable unit dosage forms accordingly comprise:

1) from about 0.01 to about 2.5 mg;
2) from about 0.25 to about 5.0 mg; and
3) from about 0.25 to about 20.0 mg,

(according to intended utility) of compound of formula I together with one or more pharmaceutically acceptable diluents or carriers therefore.

The compound of formula I may be administered as such or in the form of its pharmaceutically acceptable acid addition salts. Such salts exhibit the same order of activity as the free bases.

The compound of formula I may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of tablets or capsules, or parenterally e.g. in the form of injectible solutions or suspensions.

In accordance with the foregoing the present invention also provides:

1) A pharmaceutical composition comprising the compound of formula I I as hereinbefore defined or a pharmaceutically acceptable

acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor;

2) The compound of formula I as hereinbefore defined or pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical, i.e. for use as a neuroleptic; and especially for use in any of the specific indications hereinbefore recited in relation to such use; as well as

3) A method of effecting neuroleptic treatment,

e.g. for treating any of specific conditions hereinbefore recited in relation to such treatment, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of the compound of formula I as hereinbefore defined or a pharmaceutically acceptable acid addition salt thereof.

COMPARATIVE EXAMPLE 1

The compound of formula I falls under the scope of Australian Patent Specification 505314. The closest compound to the compound of formula I is Example 12 compound of Australian Patent Specification 505314 bearing a pivaloylamino group in 8-position and being unsubstituted in 2-position (hereinafter referred to as compound D), since it has the same substituents in 6- and 8-positions and the Australian specification suggests the equivalence of hydrogen and halogen substituents. A comparison has been effected in the inhibitory activity of apomorphine-induced climbing in the mouse.

In this test the compounds are tested for their ability to inhibit the action of 1 mg/kg s.c. apomorphine over 1 hour. The test is effected as follows:

Experiments were performed on groups of 10 male OF-1 mice weighing 22-24 g. The mice were individually housed in wire mesh climbing cages (12x12x20 cm) 30 min after oral administration of one of several doses of test drug. Apomorphine 1.0 mg/kg s.c., was administered 15 minutes later and stereotypic climbing behaviour assessed on an all or none basis every 5 min for 1 hour. Climbing was regarded as being present when the animals were suspended from the sides of the cage, or when they adopted a stationary rearing posture with both forepaws on the cage side. ED_{50}'s were calculated by the method of J.T. Litchfiled and F. Wilcoxon, J.Pharmacol.Exp. Therap. 96 99 (1949) based upon the drug effects 15 min after apomorphine application. The ED_{50} is the dose completely preventing climbing activity in 50% of the animals. The following results were obtained:

TABLE 1

Inhibition of apomorphine-induced climbing in the mouse

Compounds	ED_{50} (95% C.L.) mg/kg p.o. pre-treatment time 1h
I	0.17 (0.08-0.36
D	0.70

C.L. = confidence limits

Compound I is surprisingly an unexpectedly more active than compound D as indicated by the compound I being about 4 times more active than compound D in this test.

COMPARATIVE EXAMPLE 2

A further comparison has been effected in the inhibitory activity of the apomorphine-induced gnawing in the rat. This test is based on that of P.A. Janssen et al.,

Arzneim.-Forsc. (Drug Res.) 10, 1003-1005 (1960):

Groups of 3-4 male rats (140-180 g, Wistar) were treated with the test-drug intraperitoneally and after various pre-determined times further treated with 10.0 mg/kg s.c. apomorphine hydrochloride in aq. solution. They were then placed in individual perspex cages (Makrolon, type III) lined with corrugated paper. Animals were examined for the presence or absence of compulsive gnawing behaviour between 30 and 40 minutes after apomorphine administration, and the findings expressed as a percentage of the activity shown by vehicle pretreated controls. The supra-maximal dose of apomorphine employed invariably produced gnawing in all controls at this observation time.

The results are given in Table 2.

TABLE 2

% Inhibition of apomorphine-induced gnawing in the rat at various times after administration of the test compounds

Compound	Dose mg/kg i.p.	1h	2h	3h	3 1/2h	4h	4 1/2h	5h	5 1/2h	6h
I	0.32	100	100	100			100	65		0
	3.2	100	100	100			100		100	100
D	3.2	78	16	0						
	10	100	60	0						

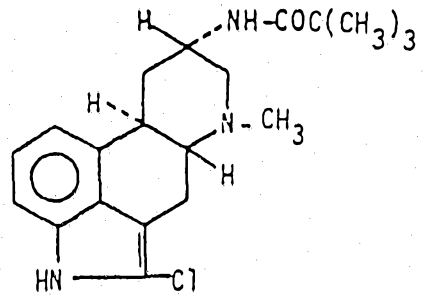
Compound I surprisingly and significantly more than 10 times more active than compound D as indicated, for example by compound I inducing 100% inhibition after 1

hour with a dose of 0.32 mg/kg i.p. whereas after 1 hour compound D induces only 78% inhibition at 3.2 mg/kg i.p. and 100% inhibition at 10 mg/kg i.p..

Compound I has surprisingly and significantly a longer duration of action than compound D as indicated by compound I exhibiting at 0.32 mg/kg i.p. and 3.2 mg/kg i.p. a 100% inhibition for at least $4\frac{1}{2}$ and 6 hours respectively, whereas compound D even at the higher dose of 10 mg/kg i.p. induces no detectable inhibition at 3 hours.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The compound of formula I

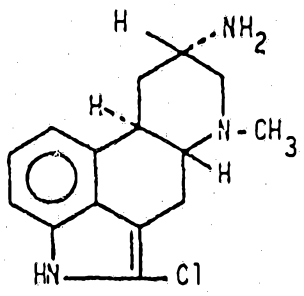


(I)

or acid addition salt thereof.

2. Process for the production of the compound of formula I as defined in claim 1 or acid addition salt thereof, which process comprises:

a) reacting a compound of formula II



(II)

with the compound of formula III

(III)

or a reactive functional derivative thereof or

b) chlorinating the compound of formula Ia

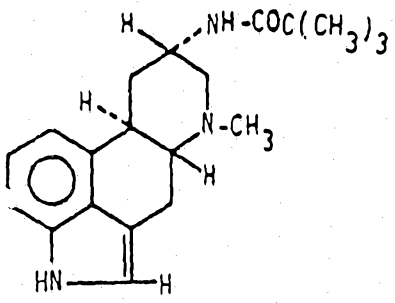
acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor;

2) The compound of formula I as hereinbefore defined or pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical, i.e. for use in therapy, for example: for use as an PRL secretion inhibitor or for use as a dopamine agonist; or for use as an LH secretion inhibitor; or for use as a neuroleptic; and especially for use in any of the specific indications hereinbefore recited in relation to such use; as well as

3) A method of

3.1.a inhibiting PRL secretion;
3.1.b treating Morbus Parkinson;
3.2 inhibiting LH secretion; or
3.3 effecting neuroleptic treatment,

e.g. for treating any of specific conditions hereinbefore recited in relation to such treatment, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of the compound of formula I as hereinbefore defined or a pharmaceutically acceptable acid addition salt thereof.



(Ia)

and recovering the obtained compound of formula I as such or as an acid addition salt thereof.

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

4. A pharmaceutical composition comprising the compound as defined in claim 1 or pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

5. A method for inhibiting prolactin secretion, treating Morbus Parkinson, inhibiting luteinizing hormone secretion or effecting neuroleptic treatment in a subject in need of such treatment, which comprises administering to said subject an effective amount of the compound of formula I or a pharmaceutically acceptable acid addition salt thereof.

6. The compound of formula I, methods for its manufacture or pharmaceutical compositions or methods of treatment involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 4th day of February, 1991
Sandoz Ltd.
By Its Patent Attorneys
DAVIES & COLLISON