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PATENT SPECIFICATION

(11) 1 573 621

- (21) Application No. 48/76 (22) Filed 2 Jan. 1976
(23) Complete Specification filed 23 Dec. 1976
(44) Complete Specification published 28 Aug. 1980
(51) INT CL³ C07D 457/12; A61K 31/48
(52) Index at acceptance

C2C 1364 1530 213 215 220 22Y 247 250 251 252 25Y 28X 29X
29Y 30Y 311 313 314 31Y 337 339 340 34Y 385 511
514 51X 51Y 520 527 531 535 539 577 627 695 72Y
802 80Y AA SC SD

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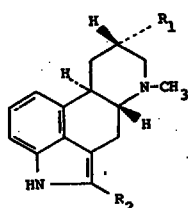
(54) ACYLATED 6-METHYL-8-AMINO-ERGOLINE I COMPOUNDS

(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 ergolines.

British Patent No. 1,517,971 discloses a class of compounds of formula I. It has now been found that certain compounds of this class not specifically disclosed therein, have particularly interesting properties.

The present invention provides compounds of formula I,



wherein R₁ and R₂ are:—

R ₁	R ₂
—NH—SO ₂ —N(Et) ₂	H
—NH—SO ₂ —3—pyridyl	H
—NH—SO ₂ —phenyl	H
—NH—SO ₂ —CF ₃	H
—NH—SO ₂ —Me	H, or
—NH—SO ₂ —N(CH ₃) ₂	Br

A compound of formula I may be produced by acylating 6-methyl-8-α-amino-ergoline I.

The compounds of formula I may be produced in analogous manner to that disclosed in the above patent.

Free base forms of the compounds of formula I may be converted into the acid addi-

tion salt forms in conventional manner and vice versa.

The starting materials are known or may be produced in known manner.

The compounds of formula I exhibit pharmacological activity in animals. In particular, 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 nigra by 6-hydroxydopamine on i.p. administration of from 1 to 40 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 scores 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 0.5 to 100

mg conveniently administered in divided doses 2 to 4 times a day in unit dosage form, containing from 0.1 to 50 mg of the compounds, or in sustained release form.

- 5 The Example 1 compound shows interesting activity.

10 Additionally, the compounds exhibit prolactin secretion inhibition activity, for example, in rats by an inhibition of ovum implantation as follows:—

- 15 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 nidations process has been interrupted [Arch. exp. Path. Pharm. 247, 367 (1967)].

20 The compounds are administered s.c. at from 0.01 to 3 mg/kg animal body weight.

- 25 For the above-mentioned use the dosage will, of course, vary depending on the compound employed, mode of administration and therapy desired. However, in general, satisfactory results are obtained when administered at a daily dosage of from 0.001 mg to 3 mg per kg animal body weight, conveniently given in divided doses 2 to 4 times a day or in sustained release form. For the larger mammal, the total daily dosage is in the range from 0.05 to 10 mg, and dosage forms suitable for oral administration comprise from 0.01 mg to 5 mg of the compounds admixed with

a solid or liquid pharmaceutical carrier or diluent.

The compounds are therefore indicated for use as prolactin secretion inhibitors. An indicated daily dose is from 0.05 to 10 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.01 to 5 mg of the compounds, 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 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 the following Examples all temperatures are in degrees Centigrade.

EXAMPLE

In a manner analogous to that disclosed in Examples 3 to 12 of the above-mentioned British Patent No. 1,517,971, the following compounds of formula I may be produced, wherein

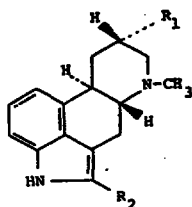
R ₁	R ₂	M.Pt.	[α] _D ²⁰ (c in DMF)
$\text{---NH-SO}_2\text{-N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$	H	201-202° ¹ 218-220° ⁴	-57° (0.3) -27° (0.4) ⁵
$\text{---NH-SO}_2\text{-} \text{pyridyl}$		262-266° ¹	-59° (0.5)
$\text{---NH-SO}_2\text{-} \text{phenyl}$	H	199-201° ¹	-55° (0.5)
$\text{---NH-SO}_2\text{-CF}_3$	H	206-208° ¹	-45° (0.45)
$\text{---NH-SO}_2\text{-CH}_3$	H	219-220° ¹ (decomp.)	-69° (0.5)
$\text{---NH-SO}_2\text{-N} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$	Br	253-256° ⁴ (decomp.)	+7° (0.5)

¹ base² hydrochloride + 1 mol H₂O³ hydrogen tartrate⁴ hydrochloride⁵ in pyridine instead of DMF

WHAT WE CLAIM IS:—

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

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wherein R₁ and R₂ are:—

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$$\begin{aligned} &\text{---NH-SO}_2\text{-N(Et)}_2 \\ &\text{---NH-SO}_2\text{-3-pyridyl} \\ &\text{---NH-SO}_2\text{-phenyl} \\ &\text{---NH-SO}_2\text{-CF}_3 \\ &\text{---NH-SO}_2\text{-Me} \\ &\text{---NH-SO}_2\text{-N(CH}_3)_2 \end{aligned}$$

$$\begin{aligned} &\text{R}_2 \\ &\text{H} \\ &\text{H} \\ &\text{H} \\ &\text{H} \\ &\text{H, or} \\ &\text{Br} \end{aligned}$$

$$\text{---NH-SO}_2\text{-N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases} \text{ and H.}$$

6. A compound of claim 4, wherein R₁ and R₂ are respectively

which comprises acylating 6-methyl-8α-amino-ergoline I.

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

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 R₁ and R₂ are respectively

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R ₁	R ₂	M.P.t.	[α] _D ²⁰ (c in DMF)
$\text{---NH-SO}_2\text{-N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$	H	201-202 ^{o1} 218-220 ^{o4}	-57° (0.3) -27° (0.4) ⁵
$\text{---NH-SO}_2\text{-} \text{C}_5\text{H}_4\text{N}$		262-266 ^{o1}	-59° (0.5)
$\text{---NH-SO}_2\text{-} \text{C}_6\text{H}_5$	H	199-201 ^{o1}	-55° (0.5)
$\text{---NH-SO}_2\text{-CF}_3$	H	206-208 ^{o1}	-45° (0.45)
$\text{---NH-SO}_2\text{-CH}_3$	H	219-220 ^{o1} (decomp.)	-69° (0.5)
$\text{---NH-SO}_2\text{-N} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$	Br	253-256 ^{o4} (decomp.)	+7° (0.5)

¹ base

² hydrochloride + 1 mol H₂O

³ hydrogen tartrate

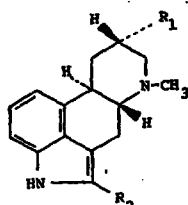
⁴ hydrochloride

⁵ in pyridine instead of DMF

WHAT WE CLAIM IS:—

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

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I

wherein R₁ and R₂ are:—

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$$\begin{aligned} &\text{---NH-SO}_2\text{-N(Et)}_2 \\ &\text{---NH-SO}_2\text{-3-pyridyl} \\ &\text{---NH-SO}_2\text{-phenyl} \\ &\text{---NH-SO}_2\text{-CF}_3 \\ &\text{---NH-SO}_2\text{-Me} \\ &\text{---NH-SO}_2\text{-N(CH}_3)_2 \end{aligned}$$

$$\begin{aligned} &\text{R}_2 \\ &\text{H} \\ &\text{H} \\ &\text{H} \\ &\text{H} \\ &\text{H, or} \\ &\text{Br} \end{aligned}$$

$$\text{---NH-SO}_2\text{-N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases} \text{ and H.}$$

which comprises acylating 6-methyl-8α-amino-ergoline I.

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

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 R₁ and R₂ are respectively

6. A compound of claim 4, wherein R₁ and R₂ are respectively

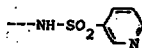
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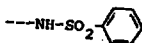


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and H.

7. A compound of claim 4, wherein R_1 and R_2 are respectively

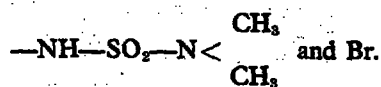


and H.

8. A compound of claim 4, wherein R_1 and R_2 are respectively $\text{---NH---SO}_2\text{---CF}_3$ and H.

9. A compound of claim 4, wherein R_1 and R_2 are respectively $\text{---NH---SO}_2\text{---CH}_3$ and H.

10. A compound of claim 4, wherein R_1 and R_2 are respectively



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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