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PATENT SPECIFICATION (11) 1 497 682

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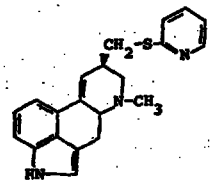
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(54) 6-METHYL-8β-(2-PYRIDYLTHIOMETHYL)ERGOLENE

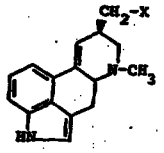
(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is ao be performed, to be particularly described in and by the following statement:—

The present invention redates to the compound 6 - methyl - 8β - (2 - pyridyl - thiomethyl)ergolene of formula I,



I

The present invention also provides a process for the production of a compound of formula I which comprises reacting a compound of formula II,



II

wherein X is an exchangeable radical capable of being displaced by a thio group,
with a compound of formula III,



III

The compound of formula I may be in free base form or in acid addition salt form.

The present process may be effected in conventional manner for nucleophilic substitution by a thio group, e.g. as described in our copending application No. 9807/75 (Serial No. 1,497,681) or in the example hereinafter.

Insofar as the production of the starting materials is not described, these are known or may be produced in accordance with known processes, or in a manner analogous to known processes.

The compound of formula I exhibits pharmacological activity. In particular it exhibits central dopaminergic stimulant activity as indicated by, for example, induction of turning in rats lesioned with 6 - hydroxydopamine in the Substantia nigra [method of U. Ungerstedt, Acta physiol. scand., Suppl. *367*, 69—93 (1971)], and additionally by an antagonism of reserpine-induced catalepsy in mice, the reserpine being administered i.p. at 5 mg/kg animal body weight about 17 hours before the test substance and the catalepsy being considered antagonised if the mice can walk off a horizontal twine covered pole in a coordinated manner.

The compounds are therefore indicated for use as anti-Parkinson agents. For this use an indicated daily dose is from 1 to 100 mg, conveniently administered in divided doses 2 to 5 times a day in unit dosage form containing from 0.2 to 50 mg, or in sustained release form.

The compound 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 form and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising the 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 composition may be made in conventional manner to be in the form of, for example, a solution or a tablet.

Additionally, the central dopaminergic stimulant activity is also observed when a compound of formula I is administered concomitantly with an inhibitor of phosphodiesterase activity, as indicated by an increase in turning movements in the above-indicated test when the compound of formula I is administered after administration of an inhibitor of phosphodiesterase activity such as caffeine.

Therefore combinations of a compound of formula I and an inhibitor of phosphodiesterase activity are also indicated for use as anti-Parkinson agents. An indicated daily dose of the compound of formula I is from 0.5 to 50 mg and an indicated ratio of formula I compound to phosphodiesterase inhibitor is from 10:1 to 1:5000, preferably 2:1 to 1:1000, e.g. 1:50 to 1:1, e.g. 1:5 to 1:1, 1:25 or 1:10 to 1:50.

Suitable phosphodiesterase inhibitors are especially those which inhibit phosphodiesterase activity in the brain, e.g. methyl xanthines such as caffeine or theophylline, but also may be chosen from derivatives of 4 - amino - 1H - pyrazolo[3,4 - b]pyridine - 5 - carboxylic acid esters, such as 1 - ethyl - 4 - (isopropylidene - hydrazino) - 1H - pyrazolo[3,4 - b]pyridine - 5 - carboxylic acid ethyl ester, 1 - ethyl - 4 - hydrazino - 1H - pyrazolo[3,4 - b]pyridine - 5 - carboxylic acid ethyl ester and 4 - butylamino - 1 - ethyl - 1H - pyrazolo[3,4 - b]pyridine - 5 - carboxylic acid ethyl ester, 4 - (3,4 - dimethoxybenzyl) - 2 - imidazolidinone and analogues thereof, such as 4 - (3 - butoxy - 4 - methoxy - benzyl) - 2 - imidazolidinone, minor tranquilizers,e. g. of the 1,4 - benzodiazepine series, such as 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - 1,4 - benzodiazepine - 4 - oxide, tricyclic anti-depressants, such as 4 - [3 - (5H - dibenz[b,f]azepin - 5 - yl)propyl] - 1 - piperazine ethanol and papaverine.

It is contemplated that all the usual pharmaceutical compositions may be made to encompass the above-indicated two active agents, e.g. tablets, powders, granulates, capsules, as well as solutions for oral administration, as well as solutions, dispersions and emulsions for parenteral administration. It is also contemplated that these compositions may be made in conventional manner using conventional pharmaceutical carriers or diluents.

A process for the production of a pharmaceutical composition includes the step of bringing the compound of formula I as one active agent into association with an inhibitor of phosphodiesterase activity as another active agent, the active agents being sufficiently pure for pharmaceutical acceptability.

It will be appreciated that combinations of a compound of formula I and a phosphodiesterase inhibitor may be conveniently administered in unit dosage form 2 to 5 times a day or in sustained release form. Such combinations may contain for example from 0.1 to 25 mg of the compound of formula I and the appropriate amount of phosphodiesterase inhibitor to give the indicated ratio range mentioned above.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade. All percentages in the Examples, except where otherwise indicated, refer to percentages by weight.

EXAMPLE 1:

6 - methyl - 8β - (2 - pyridylthiomethyl)-ergolene

4.5 g (13.5 millimols) of 6 - methyl - 8β - methane - sulphonyloxymethylergolene are heated together with 46 millimols of 2 - mercaptopyridine in a mixture of 45 cc of hexamethyl - phosphoric acid triamide and 3 cc of water to 80° under a stream of nitrogen for 20 hours. Working up is effected by pouring the reaction mixture into 450 cc of a 0.5 normal sodium carbonate solution and filtering. The dry residue is dissolved whilst hot in a mixture of methylene chloride/ether and treated with active charcoal. The filtrate is concentrated and the title compound is obtained by crystallization from ethanol in the form of pink-tinged prisms.

M.Pt. 200°—201° (decomposition).

Tartrate: M.Pt. 195°—196°; $([\alpha]_D^{20} = +26°$ (c=1, dimethyl sulphoxide).

EXAMPLE 2:

Production of a solid pharmaceutical preparation

a) 1 mg of a compound of formula I is mixed with lactose and optionally with 25 mg of a phosphodiesterase inhibitor. The mixture is granulated with water, 0.5% sodium alginate or 1% gelatin solution. The dry granulate is pressed into tablets in the presence of some tartaric acid, approx. 5% of talc, about 5% of maize starch and approx. 0.1% of magnesium stearate.

In this manner it is possible to obtain, for example, tablets having the following composition:—

Compound of formula I	1 mg	1 mg
Phosphodiesterase inhibitor	— mg	25 mg
Lactose	85.9 mg	60.9 mg
Tartaric acid	3 mg	3 mg
Maize starch	5 mg	5 mg
Talc	5 mg	5 mg
Magnesium stearate	0.1 mg	0.1 mg
	100.0 mg	100.0 mg

b) Capsules

The capsules may contain the active agent or agents alone. The following capsules may, for example, be obtained in accordance with known methods:

Compound of formula I	5 mg	5 mg
Phosphodiesterase inhibitor	50 mg	— mg
Diluent (e.g. kaolin)	— mg	295 mg
Capsule contents of	55 mg	300 mg

EXAMPLE 3

Production of a liquid pharmaceutical preparation

A liquid preparation, e.g. a suspension suitable for oral administration, may contain a compound of formula I and a phosphodiesterase inhibitor together with an inert, pharmaceutically tolerable liquid solvent or carrier material. It may further contain other additives, e.g. sweetening and colouring agent, flavourings and stabilizing agents.

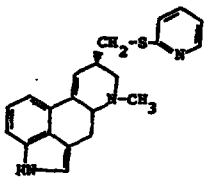
The following oral suspension may, for example, be obtained using known methods:

Compound of formula I	1.0 mg	1 mg
Phosphodiesterase inhibitor	— mg	10 mg
Vanilla assence	q.s.	q.s.
Colouring agent	q.s.	q.s.
Buffer	q.s.	q.s.
Water	q.s. up to 5 cc	q.s. up to 5 cc

The preferred phosphodiesterase inhibitors for use in Examples 2 and 3 are theophylline and caffeine.

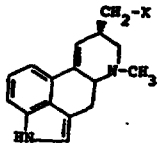
WHAT WE CLAIM IS:—

1. A process for the production of the compound 6 - methyl - 8β - (2 - pyridyl - thiomethyl)ergolene of formula I,



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which comprises reacting a compound of formula II,



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wherein X is an exchangeable radical capable of being displaced by a thio group,

with a compound of formula III,



III

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

3. The compound of formula I, whenever prepared by a process as claimed in claim 1 or claim 2.

4. The compound of formula I, as defined in claim 1, which is 6 - methyl - 8β - (2 - pyridylthiomethyl)ergolene.

5. The compound of claim 3 or 4 in free base form.

6. The compound of claim 3 or 4 in acid addition salt form.

7. A pharmaceutical composition which comprises a compound of claim 3 or 4 in

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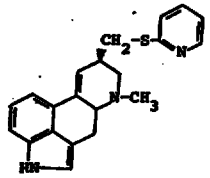
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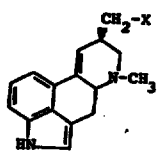
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4. The compound of formula I, as defined in claim 1, which is 6 - methyl - 8β - (2 - pyridylthiomethyl)ergolene.

5. The compound of claim 3 or 4 in free base form.

6. The compound of claim 3 or 4 in acid addition salt form.

7. A pharmaceutical composition which comprises a compound of claim 3 or 4 in

* C L M S *

free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

8. A pharmaceutical composition according to claim 7 also containing a phosphodiesterase inhibitor.

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