

AMENDED SPECIFICATION.

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PATENT SPECIFICATION

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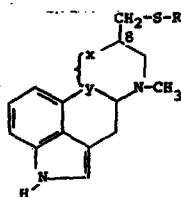
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 (72) Inventors PETER STÜTZ and PAUL STADLER

(54) THIOMETHYL ERGOLENE 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 new heterocyclic compounds.

In accordance with the invention there are provided new compounds of formula I,



I

wherein

$\begin{matrix} x \\ y \end{matrix}$ is the group —CH=C— or $\text{—CH}_2\text{—CH—}$, and

R is hydrogen, cyano, a 5- or 6-membered unsaturated heterocyclic radical attached through a ring carbon atom and having 1, 2 or 3 hetero ring atoms, the first hetero atom being nitrogen, oxygen or sulphur, and the second and third hetero atoms, if present, being nitrogen, or 2- or 4-pyridyl monosubstituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon

atoms, or chlorine, fluorine or bromine with the proviso that when $\begin{matrix} x \\ y \end{matrix}$ is —CH=C— and the side chain in the 8 position has the β configuration then R is other than 2-pyridyl.

When R is a heterocyclic radical, this is preferably fully unsaturated. R has preferably two double bonds when five-membered. R has preferably three double bonds when six-membered.

R has preferably one or two hetero atoms. When R has one hetero atom this is conveniently pyridyl or thienyl. When R has two hetero atoms, this is conveniently

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oxazolyl, thiazolyl, imidazolyl or pyrimidinyl. When R has three hetero atoms, this is conveniently 1,2,4-triazolyl, or 1,3,5-triazinyl.

The ring carbon atom through which R is attached is conveniently ortho or para to a ring hetero atom, e.g. 2-pyridyl or 4-pyridyl, 2-thiazolyl, or 1,2,4-triazol-3-yl.

When R is 2- or 4-pyridyl monosubstituted by lower alkyl, the alkyl substituent may, contain especially 1 or 2 carbon atoms and preferably signifies methyl.

When R is 2- or 4-pyridyl monosubstituted by lower alkoxy, the alkoxy substituent may, for example, contain especially 1 or 2 carbon atoms and preferably signifies methoxy.

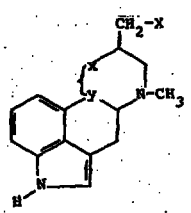
When R is 2- or 4-pyridyl monosubstituted by halogen, the halogen may denote especially chlorine.

The side chain in the 8 position of the ergolene moiety may be in the α - or β -configuration.

Any carbon containing radical not particularly defined herein preferably has up to 10 carbon atoms.

Further, in accordance with the invention a compound of formula I may be obtained by a process comprising

a) reacting a compound of formula II,



II

wherein

x y is as defined above, and

X is chlorine, bromine or a radical OSO_2R_1 , wherein R_1 is lower alkyl of 1 to 4 carbon atoms or phenyl or tolyl capable of being displaced by a thio group with a compound of formula III,



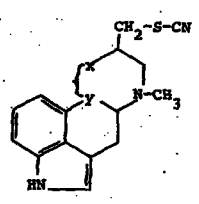
III

wherein

R is as defined above, and

M is hydrogen or an alkali metal,

or b) reducing the —SCN group to an —SH group in a compound of formula Ib,

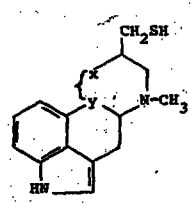


Ib

wherein

x y is as defined above,

to produce a compound of formula Ia,



Ia

wherein

x y is as defined above.

Process variant a) may be effected in conventional manner for nucleophilic substitution by a thio group, bearing in mind the other substituents present.

It is preferred to use the corresponding mesylate or tosylate as compound of formula II.

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In general M in the compounds of formula III preferably denotes an alkali metal, especially when R is not basic, i.e. has no basic nitrogen atom.

The reaction is conveniently effected in a solvent. Specially suitable are inert, aprotic, polar solvents, e.g. amides of organic carboxylic acids, such as dimethyl formamide, or alternatively hexamethylphosphoric acid triamide or acetonitrile, optionally admixed with a small portion of water.

The reaction is preferably effected at an elevated temperature, e.g. between 50 and 100°C.

The reaction is conveniently effected in the absence of oxygen, e.g. in an atmosphere of nitrogen.

It is convenient to use an excess of the compound of formula III, e.g. 2 to 10 mols of the compound of formula III, for each mol of the compound of formula II.

The reduction of compounds of formula Ib to compounds of formula Ia may be effected in a manner analogous to known methods for the reduction of similar cyanate compounds to mercapto compounds, bearing in mind the other substituents present. However, it is preferably effected with lithium aluminium hydride. In this case an ether, such as tetrahydrofuran, is especially used as solvent.

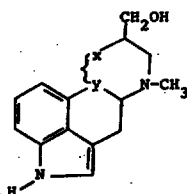
The reduction with lithium aluminium hydride may be effected at room temperature.

The working up of the reaction mixture obtained in accordance with the above processes and the purification of the so obtained compounds of formula I may be effected in accordance with known methods.

The compounds of formula I may be present in free form or in the form of acid addition salts thereof. Acid addition salt forms may be produced from the free bases in known manner and *vice versa*. A suitable acid for salt formation is tartaric or fumaric acid.

The starting materials of formula II wherein X is chlorine, O-mesyl or O-tosyl, are known.

Compounds of formula II wherein X is bromine, may, for example, be obtained by reaction of a compound of formula IV,



wherein

X Y is as defined above, with phosphorus oxybromide.

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 the processes described herein or to known processes.

The compounds of formula I exhibit pharmacological activity. In particular they exhibit 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 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 made in conventional manner to be in the form of, for example, a solution or a tablet.

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Additionally the central dopaminergic stimulant activity of a compound of formula I is also observed when administered concomitantly with an inhibitor of phosphodiesterase activity, as indicated by a superadditive increase in turning movements in the above-indicated test when a 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 further especially indicated for use as anti-Parkinson agents. An indicated daily dose of a 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-methoxybenzyl)-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 antidepressants, such as 4-[3-(5H-dibenz(b,f)azepin-5-yl)propyl]-1-piperazine ethanol, and papaverine.

The compositions may be made up into a pharmaceutical package containing as active agents a compound of formula I and an inhibitor of phosphodiesterase activity, the active agents being admixed or kept separate until required for concomitant administration.

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, syrups and elixirs 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 and diluents.

A process for the production of a pharmaceutical composition includes the step of bringing a 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 a compound of formula I and the appropriate amount of phosphodiesterase inhibitor to give the indicated ratio range mentioned above.

The compounds of formula I wherein $\overset{\text{R}}{\underset{\text{y}}{\text{C}}}=\text{CH}-$ is $-\text{CH}=\text{C}$, exhibit especially

interesting central dopaminergic stimulating properties. R preferably signifies the 2-pyridyl or cyano group.

In one group of the compounds R is hydrogen cyano or a heterocyclic as defined above. In another group of compounds R is cyano, 4-pyridyl or 2-thiazolyl.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade.

EXAMPLE 1.

6-methyl-8 β -thiocyanomethylergolene [process variant a)]

4.5 g (13.5 millimols) of 6-methyl-8 β -methanesulphonyloxymethylergolene are heated together with 4.5 g (approx. 46 millimols) of potassium thiocyanate in a mixture of 45 cc of hexamethylphosphoric 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 having a M.P. of 186—188°. Hydrogen fumarate: from methylene chloride/ethanol, M.P. 182—184°; $[\alpha]_{\text{D}}^{20} = +55^{\circ}$ (c = 0.5; dimethyl formamide).

EXAMPLE 2.

6-methyl-8 β -mercaptomethylergolene

4.5 g (approx. 60 millimols) of sodium hydrogen sulphide $\cdot$ H₂O are used in a manner analogous to that described in Example 1. After working up rapidly, the crystalline title compound is obtained from methylene chloride/isopropanol; decomposition point approx. 200°, $[\alpha]_D^{20} = +86^\circ$ ($c = 0.5$, dimethyl formamide).

The following compounds of formula I are obtained in a manner analogous to that described in Example 1, using the corresponding starting materials of formulae II and III:

EXAMPLE 3.

6-methyl-8 β -(2-pyridyl-thiomethyl)ergoline-I

M.P. 191—195°; $[\alpha]_D^{20} = -113^\circ$ ($c = 1$, pyridine).

EXAMPLE 4.

6-methyl-8 β -(4-pyridyl-thiomethyl)ergolene

M.P. 191—194°; $[\alpha]_D^{20} = +52.5^\circ$ ($c = 1$, dimethyl sulphoxide).

EXAMPLE 5.

6-methyl-8 β -(2-thiazolyl-thiomethyl)ergolene

M.P. 192—195° (decomp.); $[\alpha]_D^{20} = +58.2^\circ$ ($c = 1$, dimethyl sulphoxide).

EXAMPLE 6.

6-methyl-8 β -thiocyanomethylergoline-I

M.P. 189—193°; $[\alpha]_D^{20} = -58^\circ$ ($c = 1$, dimethyl sulphoxide).

EXAMPLE 7.

6-methyl-8 α -thiocyanomethylergoline-I

M.P. 185—188°.

EXAMPLE 8.

6-methyl-8 β -(2-thienyl-thiomethyl)ergolene

EXAMPLE 9.

6-methyl-8 β -(2-oxazolyl-thiomethyl)ergolene

EXAMPLE 10.

6-methyl-8 β -(2-imidazolyl-thiomethyl)ergolene

EXAMPLE 11.

6-methyl-8 β -(2-pyrimidinyl-thiomethyl)ergolene

EXAMPLE 12.

6-methyl-8 β -[3-(1,2,4-triazolyl)thiomethyl]ergolene

EXAMPLE 13.

6-methyl-8 β -[2-(1,3,5-triazinyl)thiomethyl]ergolene

EXAMPLE 14.

6-methyl-8 β -[2-(4-methylpyridyl)thiomethyl]ergolene

EXAMPLE 15.

6-methyl-8 β -[2-(4-methoxypyridyl)thiomethyl]ergolene

EXAMPLE 16.

6-methyl-8 β -[4-(2-chloropyridyl)thiomethyl]ergolene

EXAMPLE 17.

6-methyl-8 β -mercaptomethylergolene [process b)]

11.8 g (40 millimols) of 6-methyl-8 β -thiocyanomethyl-9-ergolene are added portionwise at room temperature to a suspension stirred under nitrogen of 15.1 g (0.4 millimols) of lithium aluminium hydride in 800 cc of absolute tetrahydrofuran, and stirring is effected for one hour at this temperature. Working up is effected by carefully decomposing with water while cooling well and stirring into 500 cc of a 5% aqueous tartaric acid solution. The reaction mixture is subsequently rendered alkaline with a potassium hydroxide solution and the aqueous phase is rapidly extracted with methylene chloride containing 10% of methanol. After drying over sodium sulphate

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and removing the solvent by distillation, the title compound is obtained. Decomp. approx. 200°, $[\alpha]_D^{20} = +86^\circ$ ($c=0.5$, dimethyl formamide).

EXAMPLE 18.

6-methyl-8 α -methanesulphonyloxymethylergoline-I

A solution of 1.95 cc (25 millimols) of methanesulphonyl chloride in 5 cc of absolute acetonitrile is added dropwise at +10° to a stirred suspension of 2.56 g (10 millimols) of 9,10-dihydro-isolysergol I [Helv. 32, 1947 (1949)] in 15 cc of absolute pyridine and 25 cc of absolute acetonitrile, and stirring is effected at room temperature for one hour. Working up is effected by cooling to 0°, diluting with methanol until a clear solution is obtained, rendering alkaline and distributing between 2N ammonia/methylene chloride. After drying and concentrating the combined organic phases by evaporation, 6-methyl-8 α -methanesulphonyloxymethylergoline-I crystallizes from ethanol.

M.P. 139—141°, $[\alpha]_D^{20} = -54.6^\circ$ ($c=1$, dimethyl formamide).

EXAMPLE 19.

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

Tablet of

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 content of

55 mg 300 mg

EXAMPLE 20.

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 agents, 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	—	10
Vanilla essence	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

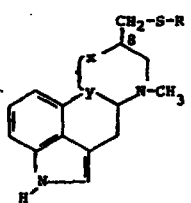
The preferred compound of formula I for use in Examples 19 and 20 is 6-methyl-8 β -thiocyanomethylergoline.

The preferred phosphodiesterase inhibitors for use in Examples 19 and 20 are theophylline and caffeine.

WHAT WE CLAIM IS:—

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

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I

5

wherein

$\overbrace{x \ y}$ is the group $-\text{CH}=\text{C}$ or $-\text{CH}_2-\text{CH}$, and

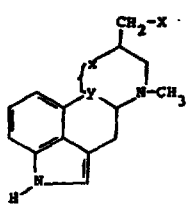
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R is a 5- or 6-membered unsaturated heterocyclic radical attached through a ring carbon atom and having 1, 2 or 3 hetero ring atoms, the first hetero atom being nitrogen, oxygen or sulphur, and the second and third hetero atoms, if present, being nitrogen, or 2- or 4-pyridyl monosubstituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms or chlorine, fluorine or bromine with the proviso that when $\overbrace{x \ y}$ is $-\text{CH}=\text{C}$ and the side chain in the 8 position has the β configuration then R is other than 2-pyridyl, which comprises

10

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a) reacting a compound of formula II,



II

wherein

$\overbrace{x \ y}$ is as defined above, and

20

X is chlorine, bromine or a radical OSO_2R_1 wherein R_1 is lower alkyl of 1 to 4 carbon atoms or phenyl or tolyl

20

with a compound of formula III,

$\text{MS}-\text{R}$

III

wherein

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R is as defined above, and M is hydrogen or an alkali metal.

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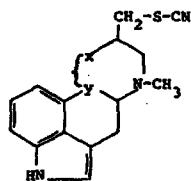
2. A process for the production of a compound of formula I stated in claim 1

wherein $\overbrace{x \ y}$ is as defined in claim 1 and R is hydrogen or cyano which comprises reacting a compound of formula II stated in claim 1 wherein $\overbrace{x \ y}$ and X are as defined in claim 1 with a compound of formula III stated in claim 1 wherein M is as defined in claim 1 and R is hydrogen or cyano.

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3. A process which comprises reducing the $-\text{SCN}$ group to an $-\text{SH}$ group in a compound of formula Ib,



Ib

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wherein

$\overbrace{x \ y}$ is as defined above,

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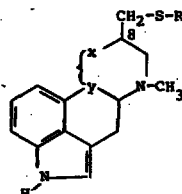
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The preferred phosphodiesterase inhibitors for use in Examples 19 and 20 are theophylline and caffeine.

WHAT WE CLAIM IS:—

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

5



I

5

wherein

$\begin{matrix} x \\ y \end{matrix}$ is the group $-\text{CH}=\text{C}<$ or $-\text{CH}_2-\text{CH}<$, and

10

R is a 5- or 6-membered unsaturated heterocyclic radical attached through a ring carbon atom and having 1, 2 or 3 hetero ring atoms, the first hetero atom being nitrogen, oxygen or sulphur, and the second and third hetero atoms, if present, being nitrogen, or 2- or 4-pyridyl monosubstituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms or chlorine, fluorine

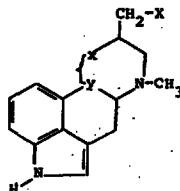
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or bromine with the proviso that when $\begin{matrix} x \\ y \end{matrix}$ is $-\text{CH}=\text{C}<$ and the side chain in the 8 position has the β configuration then R is other than 2-pyridyl, which comprises

15

a) reacting a compound of formula II,



II

wherein

20

$\begin{matrix} x \\ y \end{matrix}$ is as defined above, and

X is chlorine, bromine or a radical OSO_2R_1 wherein R_1 is lower alkyl of 1 to 4 carbon atoms or phenyl or tolyl with a compound of formula III,

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MS—R

III

wherein

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R is as defined above, and

M is hydrogen or an alkali metal.

25

2. A process for the production of a compound of formula I stated in claim 1

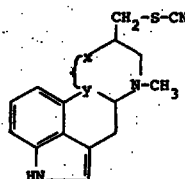
wherein $\begin{matrix} x \\ y \end{matrix}$ is as defined in claim 1 and R is hydrogen or cyano which comprises

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reacting a compound of formula II stated in claim 1 wherein $\begin{matrix} x \\ y \end{matrix}$ and X are as defined in claim 1 with a compound of formula III stated in claim 1 wherein M is as defined in claim 1 and R is hydrogen or cyano.

30

3. A process which comprises reducing the $-\text{SCN}$ group to an $-\text{SH}$ group in a compound of formula Ib,



Ib

35

wherein

$\begin{matrix} x \\ y \end{matrix}$ is as defined above,

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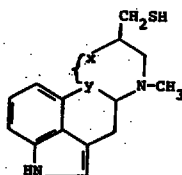


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to produce a compound of formula Ia,



Ia

wherein

x y is as defined above.

4. A compound of formula I or Ib whenever produced by a process claimed in claim 1 or 3 respectively.

5. A process for the production of a compound of formula I, as stated in Claim 1, wherein x y is as defined in claim 1 and R is hydrogen or cyano substantially as hereinbefore described with reference to Example 1 or 2.

6. A compound of formula I as stated in claim 1 wherein x y is as defined in claim 1 and R is hydrogen or cyano whenever produced by a process according to Claim 2 or 5.

7. A compound of formula I as defined in Claim 1, wherein x y and R are as defined in claim 1.

8. A compound of formula I as defined in claim 1 wherein x y is as defined in claim 1 and R is hydrogen or cyano.

9. A compound of Claim 7, wherein x y is $-\text{CH}=\text{C}$.

10. A compound of Claim 8 wherein R is CN.

11. A compound of Claim 7 wherein R is a 5- or 6-membered unsaturated heterocyclic radical as defined in claim 1.

12. A compound of Claim 7 wherein R is 2- or 4-pyridyl.

13. A compound of Claim 7 wherein R is 4-pyridyl or 2-thiazolyl.

14. A compound of Claim 7 wherein R is 1,2,4-triazol-3-yl.

15. 6-Methyl-8 β -thiocyanomethylergolene.

16. 6-Methyl-8 β -mercaptomethylergolene.

17. 6-Methyl-8 β -(2-pyridyl-thiomethyl)-ergoline-I.

18. A compound of claim 7 wherein x y is $-\text{CH}_2-\text{CH}$.

19. 6-Methyl-8 β -(4-pyridyl-thiomethyl)-ergolene.

20. 6-Methyl-8 β -(2-thiazolyl-thiomethyl)-ergolene.

21. 6-Methyl-8 β -(2-thienyl-thiomethyl)ergolene.

22. 6-Methyl-8 β -(2-oxazolyl-thiomethyl)ergolene.

23. 6-Methyl-8 β -(2-imidazolyl-thiomethyl)-ergolene.

24. 6-Methyl-8 α -(2-pyrimidinyl-thiomethyl)-ergolene.

25. 6-Methyl-8 β -[3-(1,2,4-triazolyl)thiomethyl]-ergolene.

26. 6-Methyl-8 β -[2-(1,3,5-triazinyl)thiomethyl]-ergolene.

27. 6-Methyl-8 β -[2-(4-methylpyridyl)thiomethyl]-ergolene.

28. 6-Methyl-8 β -[2-(4-methoxypyridyl)thiomethyl]-ergolene.

29. 6-Methyl-8 β -[4-(2-chloropyridyl)thiomethyl]ergolene.

30. A compound according to any one of Claims 6, 8, 10, 15 and 16 in acid addition salt form.

31. A compound according to any one of Claims 4, 7, 9, 11 to 14 and 17 to 29 in acid addition salt form.

32. A pharmaceutical composition comprising a compound according to any one of claims 6, 8, 10, 15 and 16 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

33. A pharmaceutical composition comprising a compound according to any one of Claims 4, 7, 9, 11 to 14 and 17 to 29 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

34. A pharmaceutical composition according to Claim 32 or 33, incorporating additionally a phosphodiesterase inhibitor.



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