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ERGOT PEPTIDE DERIVATIVES, THEIR PREPARATION AND PHARMA-
CEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to ergot peptide derivatives,
their preparation and pharmaceutical compositions containing
5 them.

As is known, ergot peptide alkaloids may be natural products,
modified natural products or be only obtainable by synthetic proce-
dures. Swiss Patent No 588,485 discloses the synthesis of a large
class of pharmacologically active 7-ergolene-8-carboxylic acid esters
10 and amides, including amides containing a peptide moiety
such as the cyclic tripeptide moieties in ergopeptines.
The 7-ergolene moiety may be substituted in the 2 position,
inter alia, by methyl. These methyl compounds are disclosed
as being prepared from the corresponding 8(R) ergoline
15 esters and amides. There is no suggestion in the Swiss Pa-
tent that these 8(R) ergoline derivatives have any use other
than as intermediates.

We have now found that 2-methyl-8(R) and (S) ergot
peptide alkaloids, which are nowhere specifically described
20 in or suggested by this Swiss patent, have surprisingly a
notable pharmacological profile.

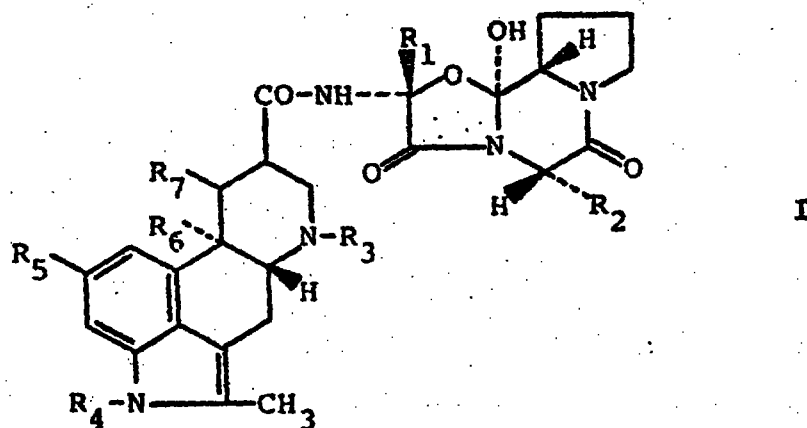
The present invention accordingly provides a 2-me-
thyl-8(R) or (S) ergot peptide alkaloid.

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These compounds are hereinafter referred to as compounds of the present invention.

It is to be appreciated that in these compounds the remaining positions of the ergot cyclic peptide alkaloid may be substituted or unsubstituted. Conveniently the ergot moiety has a double bond in the 9,10 position.

The present invention further provides a compound of formula I



wherein R_1 is (C_{1-4}) alkyl,
 R_2 is (C_{1-6}) alkyl or benzyl,
 R_3 and R_4 , independently, are hydrogen or (C_{1-4}) alkyl,
 R_5 is hydrogen or bromine,
 R_6 and R_7 are together a single bond,
 R_6 and R_7 are each hydrogen, or
 R_6 is methoxy and R_7 is hydrogen
 with the proviso that when R_5 is bromine, R_7 is hydrogen.

In Formula I R_1 is conveniently methyl or isopropyl.
 R_2 is conveniently benzyl or preferably branched alkyl e.g.
 of 3 or 4 carbon atoms. R_3 conveniently is n- or isopropyl

and preferably is methyl. R_4 is conveniently hydrogen. R_5 is preferably hydrogen. R_6 and R_7 conveniently form a single bond.

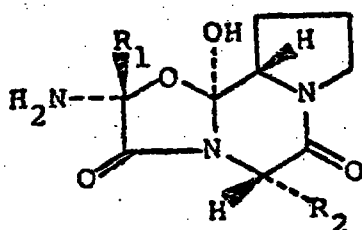
It is to be appreciated that the side chain in the 8 position of the ergot moiety may be in the α or β configuration.

The present invention in another aspect provides a process for the production of a compound of the present invention which comprises

- a) condensing an acid addition salt of an appropriate aminocyclol with a reactive acid derivative of a corresponding 2-methyl lysergic acid,
- b) reducing an appropriate ergot peptide alkaloid substituted in the 2 position with a reducible dithio-methine or thiomethylene radical capable of being reduced to a methyl group, or
- c) introducing a methyl group into the 2 position of an appropriate ergot cyclic peptide alkaloid unsubstituted in the 2 position.

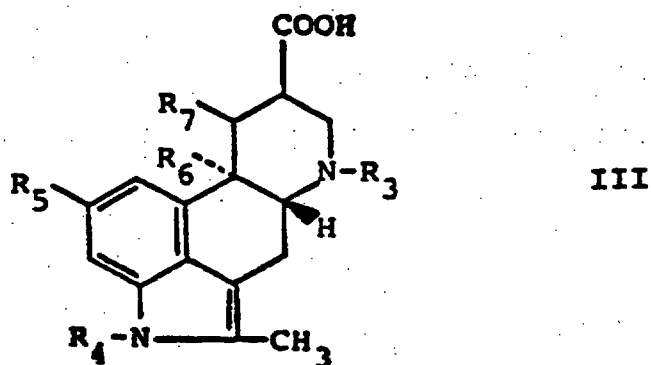
The present invention also provides a process for the production of a compound of formula I as defined above which comprises

- a) condensing an acid addition salt of a compound of formula II



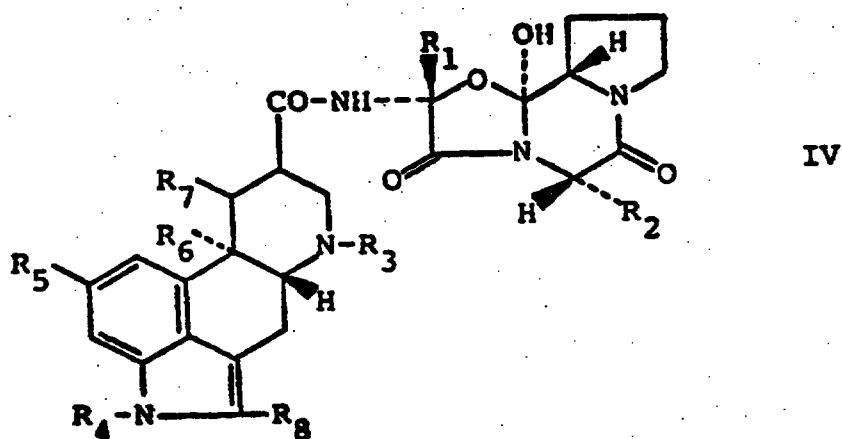
II

wherein R_1 and R_2 are as defined above
with a reactive acid derivative of a compound of formula III

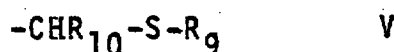


wherein R_3 to R_7 are as defined above,

5 b) reducing a compound formula IV (claimed in divisional application No. 8236817)



wherein R_1 to R_7 are as defined above,
and R_8 is a radical capable of being reduced to methyl,
of formula V

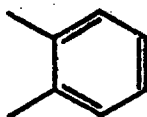


wherein R_{10} is hydrogen or a radical $-\text{S}-\text{R}_{11}$ wherein R_{11} is a benzyl radical, and

R_9 is a benzyl radical, or R_{10} is

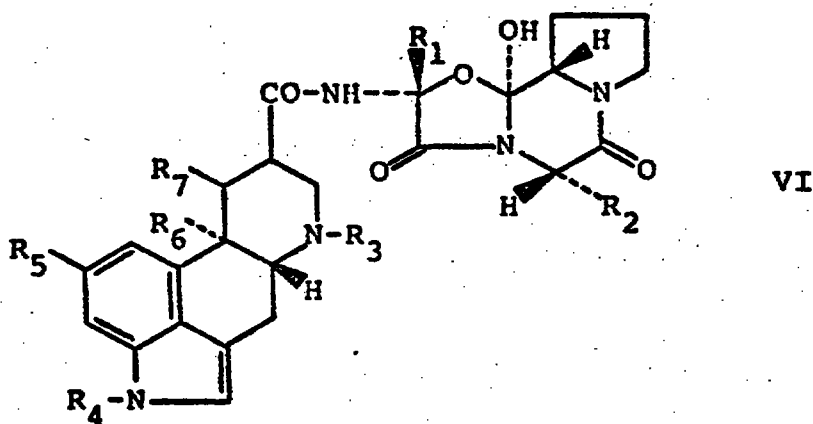
(14)

a radical $-S-R_{12}$ and R_{12} together with R_9 is a radical of formula $-(CH_2)_n-$ wherein n is 2 or 3, $-CH_2-S-CH_2-$, or



,or

c) introducing a methyl group into the 2 position of a compound of formula VI



VI

5 wherein R_1 to R_7 are as defined above.

Process a) may be effected in conventional manner for the production of analogous ergot peptide alkaloids by condensation to form the amide bond between the ergot moiety and the aminocyclol.

10 Conveniently the acid addition salt of the aminocyclol is the hydrochloride. An appropriate reactive acid derivative of the 2-methyl lysergic acid is for example the acid chloride, the acid azide, or a mixed anhydride formed from sulphuric acid or trifluoroacetic acid.

15 Alternatively the reactive acid derivative may be the addition product produced by treating the 2-methyl lysergic acid

with dimethylformamide or acetamide and thionyl chloride, phosgene, or oxalyl chloride.

Preferably the reaction is effected in the presence of triethylamine or pyridine. Suitable solvents include, for example, chloroform, methylene chloride, dimethylformamide, or acetonitrile.

The reaction is preferably effected at a temperature of from about -30°C to about $+20^{\circ}\text{C}$.

Process b) may be effected in conventional manner for analogous reductions, e.g. using catalytic conditions, particularly using Raney-Nickel of moderate activity as catalyst e.g. Raney Nickel W.6.. The reaction may be effected in solution, e.g. in a mixture of acetone/dimethylformamide.

If the catalyst is pre-treated with solvent, the reduction may be effected at room temperature. Otherwise a slightly elevated reaction temperature e.g. up to 50°C may be appropriate. It is preferred to use low temperatures when the ergot moiety has a 9,10 double bond in order to minimize saturation of this double bond.

In order to obtain a suitable catalyst to operate satisfactorily at low temperature Raney-Nickel W6 catalyst may be pre-treated by treating an aqueous suspension of Raney-Nickel W6 with an acetone/dimethylformamide mixture under stirring until dilution of a sample of the supernatant liquid with methylene chloride to twice to three times its volume does not cause any significant unclarity.

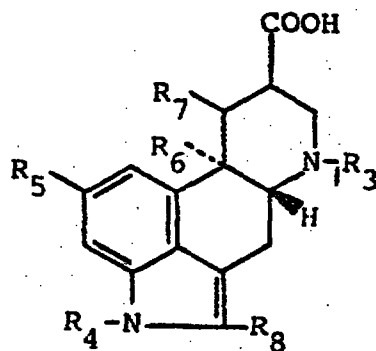
The reduction may be alternatively effected using appropriate reducing agents, e.g. sodium borohydride, lithium aluminium hydride and similar hydrides in the presence of metal salts, e.g. copper, zinc, titanium and nickel salts, in protic or aprotic solvents. A particularly suitable ^{salt} ~~reducing agent~~ is nickel boride, produced in situ, in ethylene glycol.

Preferred radicals R_8 include the 1,3-dithian-2-yl radical. Alternatively the 2-(1,3)-dithiolano radical is preferred.

Process c) may be effected in conventional manner for such methylations in analogous compounds, e.g. in a two-step reaction. For example, 9,10-dihydroergot peptide alkaloids may be substituted in the 2 position by an aminomethyl radical, and then hydrogenated.

Preferably the introduction of the methyl radical is effected in two steps, the second step of which is the same as process b). The first step of the reaction may be effected in analogous manner to the production of the starting materials for process b) described below.

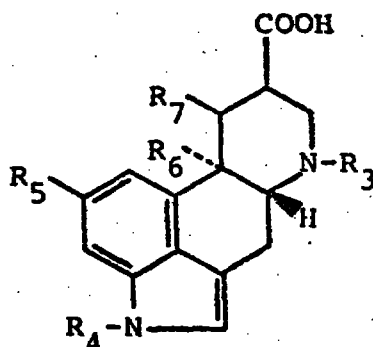
The starting materials of formula IV may be produced by condensing an acid addition salt of a compound of formula II as defined above with a reactive acid derivative of formula VII



VII

wherein R_3 to R_8 are as defined above,
for example, in analogous manner to process a).

Compounds of formula VII may for example be produced by reacting a compound of formula VIII

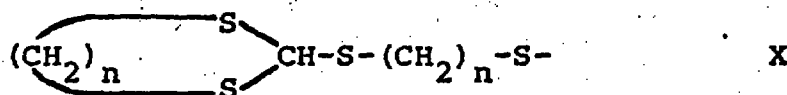


VIII

5 wherein R_3 to R_7 are as defined above
with a compound of formula IX



wherein R_8 is as defined above and L is leaving group.
The reaction may be effected in the presence of a Lewis
10 acid, e.g. titanium trichloride. The leaving group may be
e.g. chlorine, lower alkoxy, or a radical of formula X



wherein n is as defined above.

The reaction may be effected in an inert solvent,
e.g. chloroform or methanol. Suitable reaction tempera-
15 tures are from about -10 to about + 40°C.

The compounds of formula IX may be, for example,

2-methoxy-1,3-dithiolane, 2-chloro-1,3-dithiane, or 1,2-bis-(1,3-dithiolan-2-ylthio)ethane. The first two compounds are conveniently produced in situ. The use of in situ 2-chloro-1,3-dithiane (see J.Org.Chem. 44 (1979) 1847) facilitates the introduction of the 1,3-dithianyl moiety under mild conditions and without Lewis acids. For the other two compounds a Lewis acid is conveniently used.

A compound of formula IV may alternatively be produced by reacting an appropriate ergot alkaloid with a compound of formula IX as defined above, e.g. 2-chloro-1,3-dithiane, but in the absence of a Lewis acid [see Example 18].

Insofar as the production of any starting material is not particularly described then these are known or may be produced in known manner or in analogous manner to that described herein. In particular starting materials for process b) other than compounds of formula IV may be produced in analogous manner to that described above for the production of compounds of formula IV.

The compounds of the invention may be isolated from the reaction mixture, and purified, in conventional manner. When the ergot moiety has a double bond in the 9,10 position, isomerization may occur at the 8 position, particularly when contact with polar aprotic solvents.

Mixtures of 8R and 8S isomers may be separated in conventional manner, for example, by chromatography. If desired, these 8R and 8S compounds may be epimerized in

conventional manner, e.g. by treating with 2N sulphuric acid.

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

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

EXAMPLE 1: 2-methyl- α -ergocryptine and 2-methyl- α -ergo-
cryptinine (process a)

2.82 g (10 mMol) anhydrous 2-methyl lysergic acid
are dissolved in 25 ml absolute dimethylformamide on the
5 addition of 2.28 g (20 mMol) trifluoroacetic acid, and
with stirring brought to -10°C . At this temperature, a mix-
ture of 2.52 g (12 mMol) trifluoroacetic acid anhydride
in 12 ml absolute acetonitrile is added dropwise and the
resultant clear solution is stirred for 10 minutes. 12 ml
10 pyridine and 1.81 g (5 mMol) (2R,5S,10aS,10bS)-2-amino-5-
isobutyl-10b-hydroxy-2-isopropyl-octahydro-3,6-dioxo-8H-
oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine hydrochloride are
added and the reaction mixture is stirred for 1 hour at
between -10° and 0° .

15 To work up, 200 ml methylene chloride is added and
the mixture is well shaken with 100 ml 2N sodium carbonate
solution. The organic phase is separated and the aqueous
phase is washed three times with 100 ml methylene chloride.
The combined organic phase are dried over sodium sulphate
20 and concentrated in a vacuum. The residue is chromatographed
on silicagel eluted with 2% methanol in methylene chloride
to give pure 2-methyl- α -ergocryptinine. M.pt. $225-227^{\circ}$ (de-
comp) from methylene chloride/ether; $[\alpha]_{\text{D}}^{20} = + 412^{\circ}$ (c =
0.4 in chloroform).

25 Elution with 3% methanol in methylene chloride
yielded 2-methyl- α -ergocryptine. The hydrogen fumarate is
obtained by reaction with 1 equivalent of fumaric acid. M.
pt. $181-184^{\circ}$ (decomp) $[\alpha]_{\text{D}}^{20} = + 25.0$ (c=0.2 in ethanol).

The following compounds are produced in analogous manner to Example 1.

EXAMPLE 2: 2-methyl-ergotaminine

Crystallization from methylene chloride/ether.

5 M.pt. 219-221° (decomp); $[\alpha]_D^{20} = + 398^\circ$ (c = 1.0 in chloroform).

EXAMPLE 3: 2-methyl-ergotamine

Crystallization from methylene chloride/benzene.

10 M.pt. 169-171° (decomp); $[\alpha]_D^{20} = -100^\circ$ (c = 1.0 in chloroform).

EXAMPLE 4: 1,2-dimethyl-ergotamine

Crystallization as the hydrogen tartrate from abs. ethanol. M.pt. 178-179° (decomp); $[\alpha]_D^{20} = + 44^\circ$ (c = 1.0 in dimethyl formamide).

15 EXAMPLE 5: 2-methyl-6-nor-6-isopropyl-9,10-dihydroergotamine

Crystallization from methanol. M.pt. 172° (decomp); $[\alpha]_D^{20} = -60.2^\circ$ (c = 1.3 in methylene chloride).

EXAMPLE 6: 2-methyl-9,10-dihydro- β -ergocryptine

20 Crystallization from methylene chloride/ether. M.pt. 187-190° (decomp); $[\alpha]_D^{20} = -3.8^\circ$ (c = 0.4 in chloroform).

EXAMPLE 7: 2-methyl-9,10-dihydroergotamine

25 Crystallization from methylene chloride/ethyl acetate. M.pt. 185-186° (decomp); $[\alpha]_D^{20} = -77.5^\circ$ (c = 1.0 in pyridine).

EXAMPLE 8: 2-methyl-9,10-dihydroergocristine

Crystallization as the hydrogen fumarate from

methylene chloride/ethyl acetate. M.pt. 191-192°; $[\alpha]_D^{20} = -13.9^\circ$ (c = 0.6 in methanol).

EXAMPLE 9: 2-methyl-9,10-dihydro-ergonine

Crystallization from methylene chloride/benzene.

5 M.pt. 174-176° (decomp); $[\alpha]_D^{20} = -57^\circ$ (c = 0.1 in pyridine).

EXAMPLE 10: 2-methyl-9,10-dihydro-ergocornine

Crystallization from methylene chloride/benzene.

M.pt. 172-174° (decomp); $[\alpha]_D^{20} = -58^\circ$ (c = 1.0 in pyridine).

EXAMPLE 11: 2-methyl-9,10-dihydro- α -ergocryptine

10 Crystallization from methylene chloride/ether.

M.pt. 179-182° (decomp); $[\alpha]_D^{20} = 2.4^\circ$ (c = 0.55 in chloroform).

EXAMPLE 12: 2-methyl-2' β -isopropyl-5' α -n-butyl-ergopeptine

Crystallization as the hydrogen fumarate from

15 ethyl acetate/acetone. M.pt. 157-160° (decomp); $[\alpha]_D^{20} = +54.0^\circ$ (c = 0.55 in dimethylformamide).

EXAMPLE 13: 2-methyl-ergocristine

Crystallization from methylene chloride/isopropyl-

20 ether. M.pt. 165-168° (decomp); $[\alpha]_D^{20} = +40.9^\circ$ (c = 0.45 in dimethylformamide).

EXAMPLE 14: 2-methyl- β -ergocryptine

Crystallization from methylene chloride/isopropyl-

ether. M.pt. 177-180° (decomp); $[\alpha]_D^{20} = +30.0^\circ$ (c = 0.53 in dimethylformamide).

25 EXAMPLE 15: 2-methyl-ergocornine

Crystallization as the hydrogen fumarate from ethyl

acetate/ethanol. M.pt. 186-189° (decomp); $[\alpha]_D^{20} = +40.7^\circ$ (c = 0.59 in dimethylformamide).

EXAMPLE 16: 2-methyl-6-demethyl-2' β -isopropyl-5' α -isobutyl-ergopeptine

Crystallization from methylene chloride/ether.

M.pt. 172-175° (decomp); $[\alpha]_D^{20} = + 60.0^\circ$ (c = 0.21 in dimethylformamide).

EXAMPLE 17: 2-methyl-6-demethyl-6-ethyl-2' β -isopropyl-5' α -isobutyl-ergopeptine

Crystallization as the hydrogen sulfate from ethyl acetate/ether. M.pt. 142-147° (decomp); $[\alpha]_D^{20} = + 43.2^\circ$ (c = 0.45 in dimethylformamide).

EXAMPLE 18: 2-methyl- α -ergocryptine (process b. or c)

a) 2-(1,3-dithian-2-yl)- α -ergocryptine

A solution of 11.5 g (20 mMol) of α -ergocryptine in absolute chloroform _____ is added dropwise quickly to a vigorously stirred solution of about 1.2 equivalents of 2-chloro-1,3-dithiane in absolute chloroform _____ cooled to -15°. The reaction mixture is allowed to warm to 5 to 10° resulting in a black dirty precipitate. The mixture is stirred at 10° and worked up. Working up comprises making the mixture alkaline with 2N sodium carbonate solution and extracting with methylene chloride/methanol (9:1). The organic phases are washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate, filtered and evaporated. 16.7 g of a foam containing the heading compound is obtained which can be used further as such or else chromatographed on silicagel using 2% CH₃OH in CH₂Cl₂ as eluant to yield the heading compound. The hydrogen maleate of the heading compound has M.pt 163-

165° (from ethyl acetate/ether); $[\alpha]_D^{20} = + 111^\circ$ (c = 0.55 in dimethylformamide).

b) 2-methyl- α -ergocryptine

105 ml
23 ml of an aqueous suspension of Raney Nickel W6
15 repeatedly washed with 100 ml amounts of acetone/
5 ~~is pretreated with increasing amounts of 2 litres acetone/~~
~~dimethylformamide (7:3) solution under stirring.~~ dimethylformamide (8:2). Samples
of the supernatant liquid are taken as the acetone/dime-
thylformamide is added. When the sample on treatment
with methylene chloride yields no unclarity, then the
10 ~~washing with~~
~~addition of~~ acetone/dimethylformamide is stopped.

7.5 g of 2-(1,3-dithian-2-yl)- α -ergocryptine in
150 ml acetone containing 20% dimethylformamide are
treated with 105 ml of this treated Raney Nickel W6 in 100
ml of the same solvent. After 15 minutes, the catalyst
15 is filtered off and it is washed several times with about
300 ml of the solvent mixture. The solvent is distilled
from the combined organic phases to give a brown foam
which is taken up in ethanol and reacted with fumaric acid
(1 equivalent) to give the hydrogen fumarate of the heading
20 compound. M.pt. 181-184° (decomp); $[\alpha]_D^{20} = + 25.1$ (c = 0.2
ethanol).

In analogous manner, the title compounds of Examples
2 to 17 may be produced.

EXAMPLE 19: 2-methyl-6-nor-6-isopropyl-9,10-dihydro-ergo-
25 tamine (process b)

a) 2-[2-(1,3)-dithiolane]-6-nor-6-isopropyl-9,10-dihydro-
ergotamine

60 ml absolute dimethylformamide at -20° are treated

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dropwise with 2.7 g oxalyl chloride in 8.5 ml acetonitrile, and then with 7.1 g (17.7 ml mMol) dry 2-[2-(1,3)-dithiolano]-6-nor-6-isopropyl-9,10-dihydro-lysergic acid, resulting in a dark brown precipitate. The mixture is cooled to 5 0° for 30 minutes, diluted with 18 ml absolute pyridine and treated with 3.24 g (8.8 mMol) (2R,5S,10aS,10bS)-2-amino-5-benzyl-10b-hydroxy-2-methyl-octahydro-3,6-dioxo-8H-oxazolo[3,2-a]-pyrrolo[2,1-c]pyrazine hydrochloride. The mixture is stirred vigorously for 2 hours at -10° and 10 allowed to warm to 0°.

To work up, the mixture is treated with citrate buffer pH4, and made alkaline with 2N sodium carbonate solution. After extraction with methylene chloride, drying and concentration of the methylene chloride extracts, chromatography on silicagel yields the heading compound which 15 is used further as such.

b) 2-methyl-6-nor-6-isopropyl-9,10-dihydroergotamine

3.8 g sodium borohydride in 50 ml water is slowly dropped into a solution of 3.58 (5 mMol) 2-[2-(1,3)-thiolano]-6-nor-6-isopropyl-9,10-dihydro-ergotamine and 11.9 g 20 Nickel chloride hexahydrate in 120 ml of ethylene glycol. The mixture is warmed to 90° for 2 hours. The resultant black suspension is decanted and the filtrate extracted with methylene chloride.

25 The organic extracts are washed with water, dried and concentrated to give a whitish foam which is chromatographed on silicagel to give with 3% CH₃OH in CH₂Cl₂ the heading compound. M.pt. 172° (decomp; from CH₃OH);

(26)
 $[\alpha]_D^{20} = -60.2^\circ$ ($c = 1.3$ in CH_2Cl_2).

In analogous manner the compounds of Examples 1 to 4 and 6 to 17 may be produced.

The compounds of the invention exhibit pharmacological activity in animals.

5 The compounds of the invention exhibit a dopaminergic stimulating effect as indicated in standard animal tests, for example, when administered at from about 0.03 to about 3 mg/kg ^{in the} 6-hydroxydopamine rotation test of U. Ungerstedt Acta physiol. scand. Suppl. 367, 69-93 (1971).

10 The compounds are therefore indicated for use as anti-parkinson agents for e.g. for the treatment of Morbus Parkinson.

15 As indicated daily dosage is in the range from about 0.5 to about 100 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.1 mg to about 50 mg of the compounds, or in sustained release form.

20 The compounds of the invention furthermore exhibit prolactin secretion inhibitory activity, as indicated by standard tests, e.g. by inhibition of implanatation in the rat on s.c. administration of from about 0.01 to about 1 mg/kg of the compounds and an inhibition of lactation on p.o. administration of from about 1 to about 10 mg/kg of the compounds.

The compounds are therefore indicated for use as prolactin secretion inhibitors.

An indicated daily dosage is in the range from about 0.5 to about 100 mg, conveniently given in divided
5 doses 2 to 4 times a day in unit dosage form containing from about 0.1 mg to about 50 mg of the compounds, or in sustained release form.

The compounds of the invention additionally exhibit anti-depressant activity, as indicated by an inhibition of
10 ptosis and catalepsy induced by reserpine in rats on i.p. administration of 1 to 50 mg/kg of the compounds.

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

An indicated daily dosage is in the range from about
15 0.5 to about 100 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.1 mg to about 50 mg of the compounds, or in sustained release form.

The compounds of the invention furthermore exhibit
20 vigilance increasing activity as indicated by an increase in the wake phase and a decrease in the paroxodical and classical sleep phases in the sleep/wake cycle test in the rat in p.o. administration of from about 5 to about 20 mg/kg of the compounds.

25 The compounds are therefore indicated for use as vigilance increasing agents.

The compounds of the invention additionally exhibit

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ceutical diluents or carriers are those compatible with ergot alkaloids and include, for example, water, alcohols, natural or hardened oils and waxes, calcium and sodium carbonates, calcium phosphate, kaolin, talc and lactose as well as suitable preserving agents, such as ethyl-p-hydroxy-benzoate, suspending agents such as methyl cellulose, tragacanth and sodium alginate, wetting agents such as lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan mono-oleate, granulating and disintegrating agents, such as starch and alginic acid, binding agents such as starch, gelatin and acacia, and lubricating agents such as magnesium stearate, stearic acid and talc, in order to provide an elegant and palatable pharmaceutical preparation. Compositions in tablet form may be coated by conventional techniques to delay disintegration of the tablet and absorption of the active ingredient in the gastric intestinal tract and thereby provide sustained action over a long period.

21

Tablet Composition

Compound of formula I, e.g. 2-methyl-9,10-dihydro-ergo- tamine mesylate			1.025	mg
5	Tartaric acid		0.1	mg
	Lactose pulverized		84.975	mg
	Corn starch		8	mg
	Gelatine		0.3	mg
	Magnesium stearate		0.5	mg
10	Stearic acid		1.1	mg
	Talc		4	mg

The resultant composition is pressed into a 100 mg tablet.

Capsule Composition

15	Compound of formula I, e.g. 2-methyl-9,10-dihydro-ergo- tamine	1	mg
	Inert diluent (starch etc)	299	mg

The composition is filled into a hard gelatine capsule.

20 Liquid Compositions

Liquid compositions may be prepared with the following composition: -

<u>Ingredient</u>		<u>Weight (mg)</u>	
	<u>Sterile inject- able suspension</u>	<u>oral liquid suspension</u>	
25	Compound of formula I, e.g. 2-methyl-9,10- dihydroergotamine	0.5	0.5
	Sodium carboxy methyl cellulose U.S.P	1.25	12.5

	Methyl cellulose	0.4	--
	Polyvinylpyrrolidone	5	--
	Lecithin	3	--
	Benzyl alcohol	0.01	--
5	Magnesium aluminium silicate	--	47.5
	Flavour	--	q.s.
	Colour	--	q.s.
	Methyl paraben, U.S.P	--	4.5
10	Propyl paraben, U.S.P	--	1.0
	Polysorbate 80 (e.g. Tween 80), U.S.P	--	5
	Sorbitol solution, 70%, U.S.P	--	2,500
15	Buffer agent to adjust pH for desired stability	q.s.	q.s.
	Water	for injection q.s. to 1 ml	q.s. to 5 ml

In one group of compounds of formula I R_2 is (C_{1-4}) alkyl or benzyl, and R_5 is hydrogen or bromine with the proviso that (i) when R_5 is bromine R_6 and R_7 are each hydrogen, and (ii) when R_5 , R_6 and R_7 are each hydrogen, R_3 is hydrogen or (C_{2-4}) alkyl.

In a second group of compounds of formula I R_2 is (C_{1-4}) alkyl or benzyl, R_3 is methyl, and R_5 , R_6 and R_7 are each hydrogen.

In a third group of compounds of formula I R_5 is hydrogen and R_6 and R_7 together form a bond or R_6 and R_7 each are hydrogen.

In a forth group of compounds R_5 is other than

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methyl when R_5 , R_6 and R_7 are each hydrogen, and the 8 carbon atom in the ergot moiety has the R configuration.

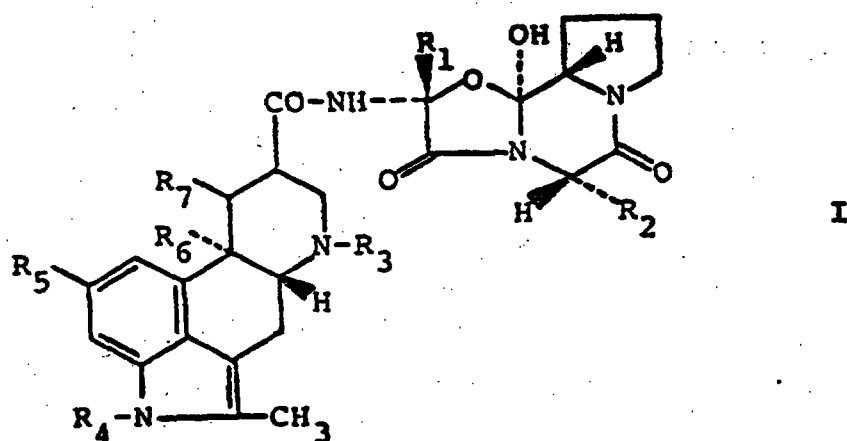
In a fifth group of compounds R_5 is methyl and R_5 , R_6 and R_7 are each hydrogen and the 8 carbon atom
5 in the ergot moiety has the R configuration.

The compound of Example 18 exhibits particularly interesting properties.



CLAIMS:

1. A 2-methyl-8(R) or (S) ergot peptide alkaloid.
2. A compound of claim 1 wherein the ergot moiety has a double bond in the 9,10 position.
- 5 3. A compound of claim 1 of formula I



wherein R_1 is (C_{1-4}) alkyl,

R_2 is (C_{1-6}) alkyl or benzyl,

R_3 and R_4 , independently, are hydrogen or (C_{1-4}) -alkyl,

10 R_5 is hydrogen or bromine,

R_6 and R_7 are together a single bond,

R_6 and R_7 are each hydrogen, or

R_6 is methoxy and R_7 is hydrogen,

with the proviso that when R_5 is bromine, R_7 is hydrogen.

- 15 4. A compound of claim 3 wherein R_3 is other than methyl when R_5, R_6 and R_7 are hydrogen and the 8 carbon atom in the ergot moiety has the R configuration.
5. A compound of claim 3 wherein R_2 is (C_{1-4}) alkyl or benzyl, and R_5 is hydrogen or bromine with the proviso

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that (i) when R_5 is bromine R_6 and R_7 are each hydrogen, and (ii) when R_5 and R_6 and R_7 are each hydrogen, R_3 is hydrogen or (C_{2-4}) alkyl.

6. A compound of claim 3 wherein R_2 is (C_{1-4}) alkyl or benzyl, R_3 is methyl, and R_5 , R_6 , and R_7 are each hydrogen.

7. A compound of claim 3 wherein R_5 is hydrogen and R_6 and R_7 together form a bond or R_6 and R_7 each are hydrogen.

8. 2-methyl-ergotaminine.

9. 2-methyl-ergotamine.

10 10. 1,2-dimethyl-ergotamine.

11. 2-methyl-6-nor-6-isopropyl-9,10-dihydroergotamine.

12. 2-methyl-9,10-dihydro- α -ergocryptine.

13. 2-methyl-9,10-dihydroergotamine.

14. 2-methyl-9,10-dihydroergocristine.

15 15. 2-methyl-9,10-dihydroergonine.

16. 2-methyl-9,10-dihydroergocornine.

17. 2-methyl-9,10-dihydro- β -ergocryptine.

18. 2-methyl-2' β -isopropyl-5' α -n-butyl-ergopeptine.

19. 2-methyl-ergocristine.

20 20. 2-methyl- β -ergocryptine.

21. 2-methyl-ergocornine.

22. 2-methyl-6-demethyl-2' β -isopropyl-5' α -isobutyl-ergopeptine.



23. 2-methyl-6-demethyl-6-ethyl-2' β -isopropyl-5' α -iso-butyl-ergopeptine.
24. 2-methyl- α -ergocryptine.
25. 2-methyl- α -ergocryptinine.
- 5 26. A compound according to any one of claims 1 to 25 in free base form.
27. A compound according to any one of claims 1 to 25 in acid addition salt form.
28. A compound according to any one of claims 1 to 25
- 10 for use as a pharmaceutical.
29. A compound according to any one of claims 1 to 25 for use as an anti-parkinson agent.
30. A compound according to any one of claims 1 to 25 for use as a vigilance increasing agent.
- 15 31. A compound according to any one of claims 1 to 25 for use as a prolactin secretion inhibitor, anti-depressant or anti-migraine agent.
32. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25 in free base form
- 20 or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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