ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

THE PATENT OFFICE OF CYPRUS

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ **CY1331**
PUBLICATION NUMBER

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
UK PATENT OFFICE
PUBLICATION NUMBER GB2053908

Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

The document provided hereafter was filed at "The Patent Office" in England under the law CAP.266 before the 1st of April 1998. It was published afterwards by the UK patent office only in English.

(12) UK Patent Application (19) GB (11) 2 053 908 A

(21) Application No 8018827
(22) Date of filing 9 Jun 1980
(30) Priority data
(31) 5476/79
(32) 12 Jun 1979
(31) 5479/79
(32) 12 Jun 1979
(31) 5478/79
(32) 12 Jun 1979
(31) 5477/79
(32) 12 Jun 1979
(33) Switzerland (CH)
(43) Application published
11 Feb 1981
(51) INT CL³
C07D 519/02 A61K
31/505
(52) Domestic classification
C2C 1364 1369 1524
1720 213 214 215 220
226 22Y 246 247 250 252
254 255 25Y 280 281
28X 29X 29Y 30Y 342
34Y 351 352 360 363 36Y
604 623 62X 672 802
80Y AA KR
(56) Documents cited
CH 588485A
(58) Field of search
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(54) Ergot Peptide Derivatives

(57) Novel 2-methyl-8 (R) or (S) ergot peptide alkaloids in free base form or in pharmaceutically acceptable acid addition salt form are useful anti-Parkinson agents, prolactin secretion inhibitors, anti-depressants, vigilance-increasing agents, and anti-migraine agents.

Intermediate ergot peptide alkaloids substituted in the 2 position by a dithiomethine or thiomethylene group which is reducable to a methyl group are also claimed.

GB 2 053 908 A

SPECIFICATION

Ergotpeptide Derivates, Their Production and Pharmaceutical Compositions Containing Them

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

As is known, ergot peptide alkaloids may be natural products, modified natural products or be only obtainable by synthetic procedures. Swiss Patent No. 588,485 discloses the synthesis of a large class of pharmacologically active 7-ergolene-8-carboxylic acid esters 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 esters and amides. There is no suggestion in the Swiss Patent that these 8(R) ergoline derivatives have any use other than as intermediates.

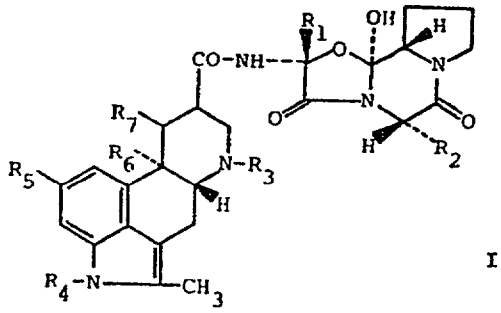
We have now found that 2-methyl-8(R) and (S) ergot peptide alkaloids, which are nowhere specifically described in or suggested by this Swiss patent, have surprisingly a notable pharmacological profile.

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

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



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

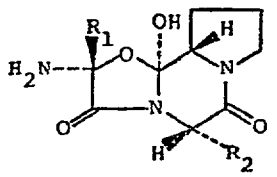
a) condensing an acid addition salt of an appropriate aminocyclol with a reactive acid derivative of a corresponding 2-methyl lysergic acid,

b) reducing an appropriate ergot peptide alkaloid substituted in the 2 position with a reducible dithiomethine 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.

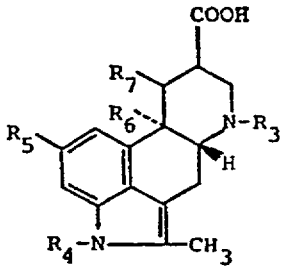
The present invention also provides a process for the production of a compound of formula I as defined above which comprises

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



II

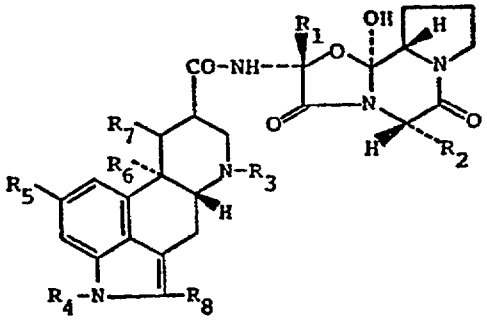
wherein R_1 and R_2 are as defined above with a reactive acid derivative of a compound of formula III



III

wherein R_3 to R_7 are as defined above,

b) reducing a compound formula IV

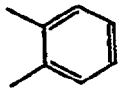


IV

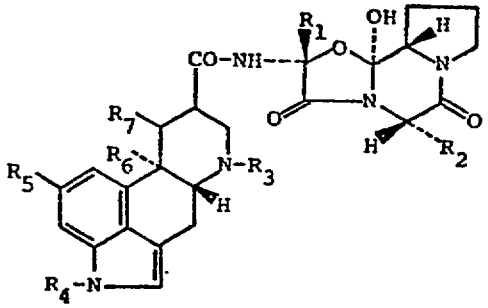
wherein R_1 to R_7 are as defined above, and R_8 is a radical capable of being reduced to methyl, of formula V

$$—CHR_{10}—S—R_9 \qquad V$$

wherein

R_{10} is hydrogen or a radical —S—R_{11} wherein R_{11} is lower alkyl or a benzyl radical, and R_9 is lower alkyl or a benzyl radical, or R_{10} is 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

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.

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.

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°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.

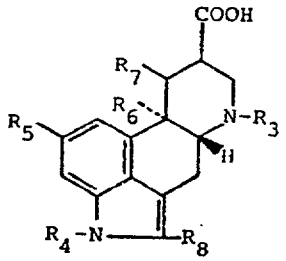
The reduction may be alternatively effected using appropriate reducing agents, e.g. sodium borohydride, lithium aluminium hydride and similar hydrides in the presence of metal salts, e.g. copper, zinc, titanium and nickel salts, in protic or aprotic solvents. A particularly suitable salt is nickel boride,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

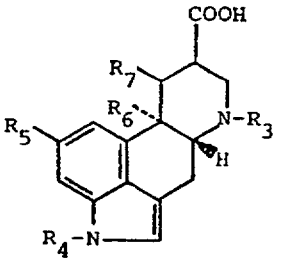
The starting materials of formula IV may be produced by condensing an acid addition salt of a compound of formula II as defined above with a reactive acid derivative of formula VII



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

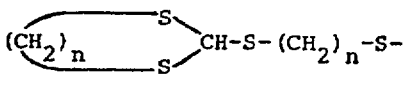


VIII

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

$$L—R_8 \qquad \text{IX}$$

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



X

wherein n is as defined above.

The reaction may be effected in an inert solvent, e.g. chloroform or methanol. Suitable reaction temperatures 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 indroduction 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-ercocryptine and 2-methyl-α-ergocryptine (process a)

2.82 g (10 mMol) anhydrous 2-methyl lysergic acid are dissolved in 25 ml absolute dimethylformamide on the addition of 2.28 g (20 mMol) trifluoroacetic acid, and with stirring brought to −10°C. At this temperature, a mixture 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 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°.

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 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° (decomp) from methylene chloride/ether; $[\alpha]_D^{20}$=+412° (c=0.4 in chloroform).

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

Example 3
2-methyl-ergotamine

Crystallization from methylene chloride/benzene. M.pt. 169—171° (decomp); $[\alpha]_D^{20}$=−100° (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° (c=1.0 in dimethyl formamide).

Example 5
2-methyl-6-nor-6-isopropyl-9,10-dihydroergotamine

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

Example 6
2-methyl-9,10-dihydro-β-ergocryptine

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

Example 7
2-methyl-9,10-dihydroergotamine
Crystallization from methylene chloride/ether acetate. M.pt. 185—186° (decomp); $[\alpha]_D^{20}$=—77.5° (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° (c=0.6 in methanol).

Example 9
2-methyl-9,10-dihydro-ergonine
Crystallization from methylene chloride/benzene. M.pt. 174—176° (decomp); $[\alpha]_D^{20}$=—57° (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° (c=1.0 in pyridine).

Example 11
2-methyl-9,10-dihydro-α-ergocryptine
Crystallization from methylene chloride/ether. M.pt. 179—182° (decomp); $[\alpha]_D^{20}$=2.4° (c=0.55 in chloroform).

Example 12
2-methyl-2'β-isopropyl-5'α-n-butyl-ergopeptine
Crystallization as the hydrogen fumarate from ethyl acetate/acetone. M.pt. 157—160° (decomp); $[\alpha]_D^{20}$=+54.0° (c=0.55 in dimethylformamide).

Example 13
2-methyl-ergocristine
Crystallization from methylene chloride/isopropyl-ether. M.pt. 165—168° (decomp); $[\alpha]_D^{20}$=+40.9° (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° (c=0.53 in dimethylformamide).

Example 15
2-methyl-ergocornine
Crystallization as the hydrogen fumarate from ethyl acetate/ethanol. M.pt. 186—189° (decomp); $[\alpha]_D^{20}$=+40.7° (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° (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° (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% CH_3OH in CH_2Cl_2 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° (c=0.55 in dimethylformamide).

b) 2-methyl-α-ergocryptine

105 ml of an aqueous suspension of Raney Nickel W6 is repeatedly washed with 100 ml amounts of acetone/dimethylformamide (8:2). Samples of the supernatant liquid are taken as the acetone/dimethylformamide is added. When the sample on treatment with methylene chloride yields no unclarity, then the washing with 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 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 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-ergotamine (process b)

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

60 ml absolute dimethylformamide at −20° are treated 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 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 allowed to worm 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 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 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.

The organic extracts are washed with water, dried and concentrated to give a whitish foam which is chromatographed on silicagel to give with 3% CH_3OH in CH_2Cl_2 the heading compound. M.pt. 172° (decomp; from CH_3OH); $[\alpha]_D^{20}$=−60.2° (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.

The compounds of the invention exhibit a dopaminergic stimulating effect as indicated in standard animal tests. For example, the compounds when administered at from about 0.03 to about 3 mg/kg inhibit the rotations induced by i.p. injection of 6-hydroxydopamine into the substantia nigra unilaterally into the nigra-neostriatala dopamine pathway [method according to U. Ungerstaedt Acta physiol. scand. Suppl. *367*, 64—93 (1973)]. The compounds also inhibit stereotypy in the apomorphine stereotypy test in i.p. administration of about 30 mg/kg of the compound.

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

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.

The compounds of the invention furthermore exhibit prolactin secretion inhibitory activity, as indicated by standard tests, e.g. by inhibition of implantation 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 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 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 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 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.

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

The compounds of the invention additionally exhibit a vasoconstricting effect in standard animal tests, e.g. in the Mellander-cat test [Angiologica *3*, 77—99 (1966)] by an arterial vasotonic effect, on i.a. administration of from about 5 to about 45 μg/kg animal body weight.

The compounds are therefore indicated for use in the treatment of migraine and orthostatic disorders.

For the above two indications, an 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 admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of the invention 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 conveniently contain more than 1% by weight of the compound of the invention and may be prepared by conventional techniques to be in conventional forms, for example, capsules, tablets, suppositories, dispersible powders, syrups, elixirs, suspensions or solutions, for enteral or parenteral administration. Suitable pharmaceutical 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, tragacanthand 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, gelatine 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.

Tablet Composition

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

The resultant composition is pressed into a 100 mg tablet.

Capsule Composition

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

The composition is filled into a hard gelatine capsule.

Liquid Compositions

Liquid compositions may be prepared with the following composition:—

Ingredient	*Sterile injectable suspension*	*Weight (mg) oral liquid suspension*
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	—
Magnesium aluminium silicate	—	47.5
Flavour	—	q.s.
Colour	—	q.s.
Methyl paraben, U.S.P.	—	4.5
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
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 fourth group of compounds R_5 is other than 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 in the ergot moiety has the R configuration.

The compound of Example 18 exhibits particularly interesting properties.

Claims

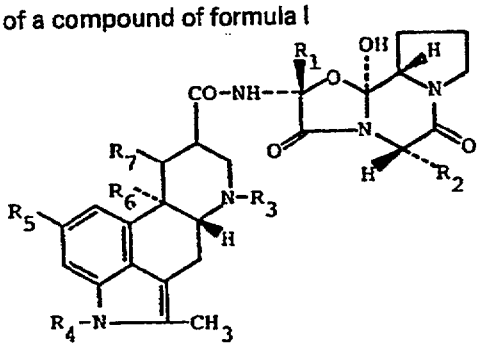
1. A process for the production of a 2-methyl-8(R) or (S) ergot peptide alkaloid which comprises

a) condensing an acid addition salt of an appropriate amino-cyclol 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 dithiomethine 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.

2. A process for the production of a compound of formula I



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,

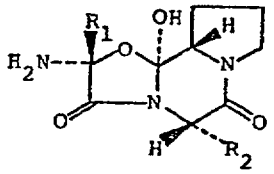
R_6 and R_7 are together a single bond,

R_6 and R_7 are each hydrogen, or

R_6 is methoxy and R_7 is hydrogen

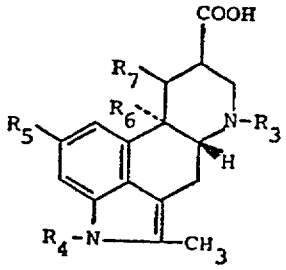
with the proviso that when R_5 is bromine, R_7 is hydrogen, which comprises

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



II

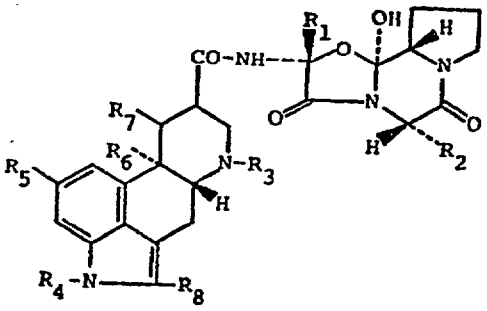
wherein R_1 and R_2 are as defined above, with a reactive acid derivative of a compound of formula III



III

wherein R_3 to R_7 are as defined above,

b) reducing a compound of formula IV,



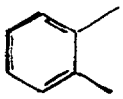
IV

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

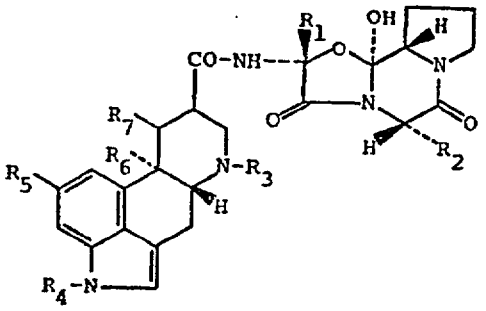
$$—CHR_{10}—S—R_9 \qquad V$$

wherein

R_{10} is hydrogen, or a radical —S—R_{11}, wherein
R_{11} is lower alkyl or a benzyl radical, and
R_9 is lower alkyl or a benzyl radical, or
R_{10} is 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

wherein R_1 to R_7 are as defined above.

3. A process for the production of a 2-methyl-8(R) or (S) ergot peptide alkaloid, substantially as hereinbefore described with reference to any one of the Examples.

4. 2-methyl-8(R) or (S) ergot peptide alkaloid, whenever produced by a process according to claim 1 or 3.

5. A compound of formula I, as defined in claim 2 whenever produced by a process according to claim 2.

6. A 2-methyl-8(R) or (S) ergot peptide alkaloid.

7. A compound of claim 6 wherein the ergot moiety has a double bond in the 9,10 position.

8. A compound of formula I as defined in claim 2.

9. A compound of claim 8 wherein R_3 is other than 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.

10. A compound of claim 8 wherein 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 and R_6 and R_7 are each hydrogen, R_3 is hydrogen or (C_{2-4})alkyl.

11. A compound of claim 8 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.

12. A compound of claim 8 wherein R_5 is hydrogen and R_6 and R_7 together form a bond or R_6 and R_7 each are hydrogen.

13. A compound of claim 8 which is 2-methyl-ergotaminine.

14. A compound of claim 8 which is 2-methyl-ergotamine.

15. A compound of claim 8 which is 1,2-dimethyl-ergotamine.

16. A compound of claim 8 which is 2-methyl-6-nor-6-isopropyl-9,10-dihydroergotamine.

17. A compound of claim 8 which is 2-methyl-9,10-dihydro-α-ergocryptine.

18. A compound of claim 8 which is 2-methyl-9,10-dihydroergotamine.

19. A compound of claim 8 which is 2-methyl-9,10-dihydroergocristine.

20. A compound of claim 8 which is 2-methyl-9,10-dihydroergonine.

21. A compound of claim 8 which is 2-methyl-9,10-dihydroergocornine.

22. A compound of claim 8 which is 2-methyl-9,10-dihydro-α-ergocryptine.

23. A compound of claim 8 which is 2-methyl-2'β-isopropyl-5'α-n-butyl-ergopeptine.

24. A compound of claim 8 which is 2-methyl-ergocristine.

25. A compound of claim 8 which is 2-methyl-β-ergocryptine.

26. A compound of claim 8 which is 2-methyl-ergocornine.

27. A compound of claim 8 which is 2-methyl-6-demethyl-2'β-isopropyl-5'α-isobutyl-ergopeptine.

28. A compound of claim 8 which is 2-methyl-6-demethyl-6-ethyl-2'β-isopropyl-5'α-isobutyl-ergopeptine.

29. A compound of claim 8 which is 2-methyl-α-ergocryptine.

30. A compound of claim 8 which is 2-methyl-6-nor-6-isopropyl-9,10-dihydro-ergotamine.

31. A compound of claim 8 which is 2-methyl-α-ergocryptinine.

32. A compound according to any one of claims 4 to 31 in free base form.

33. A compound according to any one of claims 4 to 31 in acid addition salt form.

34. A pharmaceutical composition comprising a compound according to any one of claims 4 to 31 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

35. An ergot peptide alkaloid substituted in the 2 position with a reducible dithiomethine or thiomethylene radical capable of being reduced to a methyl group.

36. A compound of formuia IV as stated in claim 2.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.