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ERGOTALKALOIDS

This invention relates to ergot peptide alkaloids.

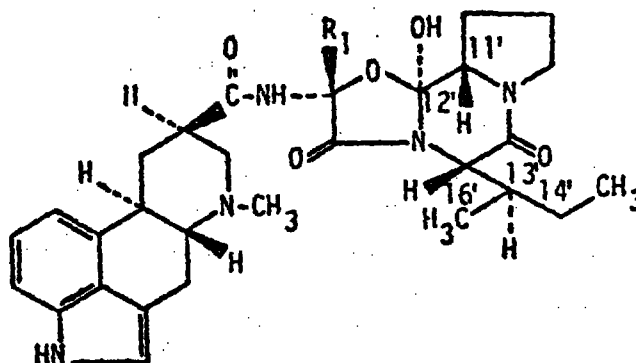
The present invention provides ergot 5'S-(2R-butyl) peptide alkaloids, hereinafter referred to as compounds of the invention, and their acid addition salts.

The ergot 5'S-(2R-butyl) compounds of the invention are hitherto totally unknown epimers of ergot peptide alkaloids, these latter alkaloids being preparable by chemical synthesis or, in some cases, also being found in nature or preparable by e.g. fermentation. They may be substituted. Furthermore, they may exist in the form of isomers, e.g. as the 8R or 8S isomers.

The chemistry of ergot peptide alkaloids has been recently reviewed in B.Berde and H.O.Schild "Ergot alkaloids and related compounds", 1978, Springer Verlag, Berlin in Chapter II, p.29 to 85 by J.Rutschmann and P.Stadler. It is accepted that the known 5'S-(2-butyl) derivatives, e.g.  $\beta$ -ergocryptine, have the S configuration in the sec-butyl side chain (see p.37 of the above mentioned B.Berde and H.O.Schild publication and also p.2468 of Dictionary of Organic Compounds, 5th edition, Volume 3 Chapman and Hall, New York, 1982). The 2-butyl carbon atom having the S configuration is known under Chemical Abstracts nomenclature used in the 8th collective index as the 13' carbon atom.

-2-

In particular the present invention provides a compound of formula I

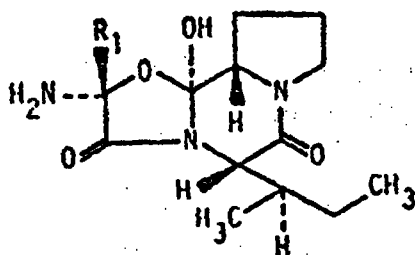


wherein R<sub>1</sub> is methyl, ethyl or isopropyl, and its acid addition salts.

- 5        The present invention in another aspect provides a process for the preparation of an ergot 5'S-(2R-butyl) peptide alkaloid or an acid addition salt thereof which includes the step of condensing an acid addition salt of a corresponding 5'S-(2R-butyl)aminocyclool with a reactive
- 10    acid derivative of a corresponding lysergic acid derivative, and recovering the resultant above mentioned compound as such or as an acid addition salt thereof.

"Aminocyclol" covers typical tripeptides having a hydroxy group used in the synthesis of ergot peptide alkaloids. For example, they are cyclic tripeptides having an amino group in the 2' position and a hydroxy group in the 12' position.

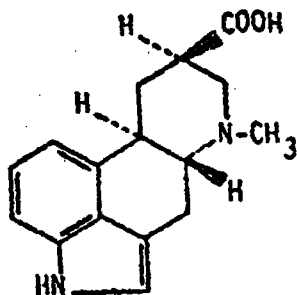
- 5 A compound of formula I may be produced by a process which includes the step of condensing an acid addition salt of a compound of formula II



II

wherein R<sub>1</sub> is as defined above,

- 10 with a reactive acid derivative of a compound of formula III



III

and recovering the resultant compound of formula I as such or as an acid addition salt thereof.

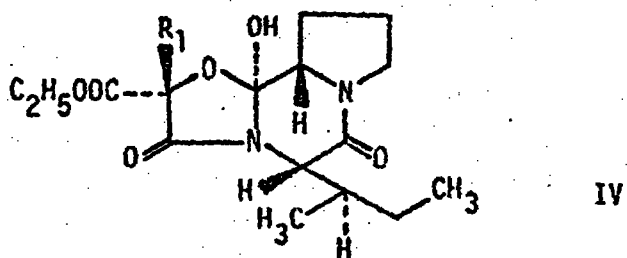
The condensation process of the invention may be effected in conventional manner for the production of analogous ergot peptide alkaloids.

An acid addition salt of the aminocyclol is for example the hydrochloride. A reactive acid derivative of the corresponding lysergic acid derivative is for example the acid chloride, or the mixed anhydride with sulfuric acid or trifluoroacetic acid. Alternatively the derivative may be the addition product produced from the corresponding lysergic acid with (i) dimethylformamide or acetamide and (ii) thionyl chloride, phosgene or oxalyl chloride. Preferably the reaction is effected in the presence of triethylamine or pyridine. Suitable solvents are for example chloroform, methylene chloride, dimethylformamide or acetonitrile. The reaction temperature may be for example from about  $-30^{\circ}\text{C}$  to  $+20^{\circ}\text{C}$ .

The lysergic acid derivative and/or aminocyclol may be in temporarily protected form.

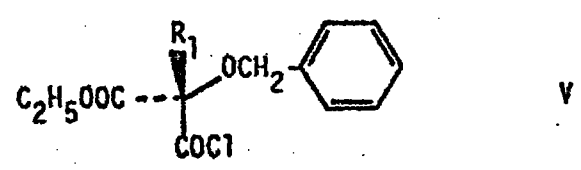
The compounds of the invention may be converted into acid addition salts thereof in conventional manner and vice versa. A suitable acid addition salt is the hydrochloride or methanesulphate.

- 5 The starting materials are known or may be produced in conventional manner from known compounds, e.g. as described below in respect of compounds of formula II which may be produced for example from compounds of formula IV

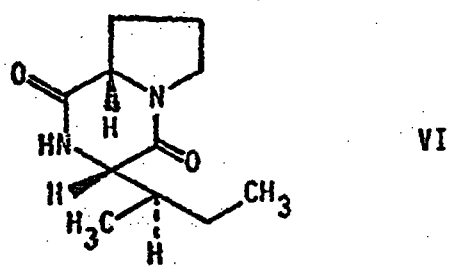


- 10 in conventional manner, e.g. via the hydrazide and benzyl ester as described in the examples.

The compound of formula IV may be produced by reacting a compound of formula V



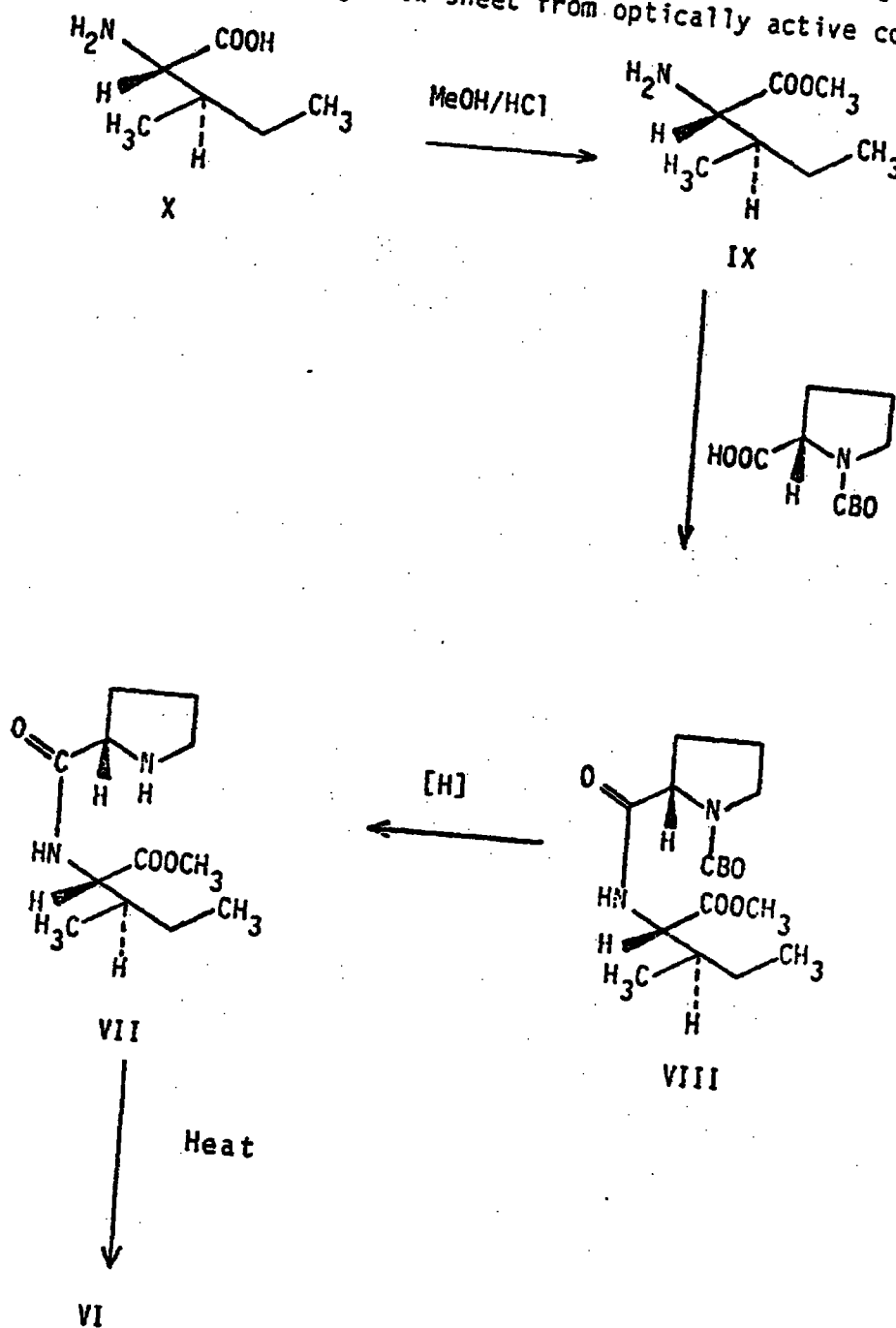
with a compound of formula VI



and hydrogenating the resultant tripeptide benzyl ether, e.g. as  
5 described in the examples.

-7-

The compound of formula VI may be produced e.g. as described in the following flow-sheet from optically active compounds:-



-8-

The aminocyclols are preferably produced in optically pure form from optically active compounds as described above. If desired some of the starting materials may be in racemic form and on reaction with an optically active starting material, the diastereoisomers may be separated in conventional manner, e.g. chromatography. For example the compound of formula VI may be separated from its epimers, e.g. produced from a mixture of isoleucine including the compound of formula X and diastereoisomers and epimers thereof obtainable from glycine.

The so-obtained compounds of the invention and their acid addition salts thereof may be isolated according to known methods and purified e.g. by high performance liquid chromatography, other chromatographic techniques or crystallisation.

The present invention in another aspect provides a compound of the invention in the presence of less than 5 % by weight, less than 2 % by weight, or less than 1 % by weight, of the corresponding 5'S-(2S-butyl) epimer, e.g. dihydro- $\beta$ -ergocryptine or an acid addition salt thereof.

The presence of an epimer may be detected by conventional analytical techniques, e.g. high performance liquid chromatography or nuclear magnetic resonance.

A compound of the invention or an acid addition salt thereof wherein  $R_1$  is isopropyl (hereinafter 5'S-(2R-butyl)), and dihydro- $\beta$ -ergocryptine (hereinafter 5'S-(2S-butyl)) may be distinguished according to n.m.r. peak shifts, according to the  $^1\text{H}$  NMR spectrum (360 MHz; solvent  $\text{CDCl}_3$ ; standard tetramethylsilane) as follows:-

| (ppm)   | 5'S-(2R-butyl) | 5'S-(2S-butyl) |
|---------|----------------|----------------|
| C-5'-H  | 4.53           | 4.50           |
| C-13'-H | 1.30           | 1.50           |

According to the  $^{13}\text{C}$  NMR spectrum (360 MHz; 30 mg/1.5 ml;  $\text{pD} = 3.4$ ) the compounds may be distinguished as follows:-

| (ppm)                  | 5'S-(2R-butyl) | 5'S-(2S-butyl) |
|------------------------|----------------|----------------|
| $\text{CH}_3$ on C-13' | 17.5           | 16.4           |
| $\text{CH}_2$ on C-13' | 27.4           | 28.6           |

Thus the presence of 1% or more of the 5'S-(2S-butyl) epimers in the compounds of the invention may be detected.

-10-

A suitable system for high performance liquid chromatography comprises a solvent system of a) 1% triethylamine in water mixed with b) 1% triethylamine in acetonitrile. The solvent system initially comprises 15% b) and this is increased to 50% b) over 20 minutes. The system is caused to flow at 2 ml/minute through a column RF 18 (Knauer) length 25 cm diameter 4.6 mm. The 5'S-(2R-butyl) compound of example 1 had a retention time of 19 minutes. Beta-dihydroergocryptine had a retention time of 20 minutes.

Another suitable solvent system is water/acetonitrile/tetramethylammonium chloride/trimethylamine (755 g : 240 g : 4 g : 1 g); solid phase LiChrosorb (registered Trademark; Merck) R 18 (particle diameter 10 mm; column diameter 16 mm; length 25 cm).

Insofar as the production of any starting material, e.g. for compounds of the invention other than those of formula I, is not particularly described, then they may be produced and purified in analogous manner to that described herein in respect of those for the compounds of formula I or in conventional manner for analogous compounds.

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

-11-

High vacuum refers to ca 0.01 mm mercury.

All optical rotations are at 20°C and at the sodium D line except where otherwise stated.

All N.M.R. shifts ( $\delta$ ) refer to ppm; m = multiplet; s = singlet; q = quartet; t = triplet.

EXAMPLE-1: (5R,8R,10R)-N-[(2R,5S,11S,12S)-5-(2R-butyl)-  
octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-  
oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-yl]-6-methyl-  
ergoline-8-carboxylic acid amide also identified as  
5 (5' $\alpha$ ,10 $\alpha$ )-9,10-dihydro-12'-hydroxy-2'-(1-methylethyl)  
-5'-[(R)-1-methylpropyl]ergotaman-3',6',18-trione  
according to Chemical abstracts 9th Collective Index  
nomenclature

1.8 ml (22.5 mM) trifluoroacetic acid is added to a mixture  
10 of 5.36 g (20 ml) anhydrous 9,10-dihydrolysergic acid  
(5R,8R,10R), 40 ml absolute dimethylformamide and 20 ml absolute  
acetonitrile. 2.8 ml trifluoroacetic acid anhydride (20 ml) and  
20 ml pyridine are added at -10°. The reaction mixture is stirred  
further for 5 minutes at -10° and then 3.62 g (10 mM)  
15 (2R,5S,11S,12S)-2-amino-5-(2R-butyl)-octahydro-12-hydroxy-2-  
isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine  
monohydrochloride is added. The reaction mixture is stirred and  
allowed to warm to 22° during 2 hours. The mixture is partitioned  
between methylene chloride and water. The organic phase is dried  
20 with sodium sulphate, filtered and concentrated. The residue is  
crystallised from ethyl acetate/ether.

M.pt. 190-191°;  $[\alpha]^{20}_D = -43.5^\circ$  (c = 0.5 in pyridine).

NMR 360 MHz (CDCl<sub>3</sub>) 0.98 ppm (6H, t), 1.08 - 1.17  
(6H, q), 1.3 (1H, m, C-13-H)

25 <sup>13</sup>C-NMR 360 MHz (30 mg/1.5 ml, pD = 3.4): No visible signal at

16.4 or 28.6 ppm that can be attributed to the epimer, dihydro- $\beta$ -ergocryptine, indicating that less than 1% of the epimer is present.

The starting material (2R,5S,11S,12S)-2-amino-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]-pyrrolo[2,1-c]pyrazine monohydrochloride is produced as follows:-

a) (3S,8aS)-3-(2R-butyl)-hexahydro-pyrrolo[1;2-a]piperazine-1;4-dione (compound of formula VI)

i) (2S,3R)-L-allo-isoleucine methyl ester.

10 30 g (229 mM) (2S,3R)-L-Allo-isoleucine ( $[\alpha]^{20}_D = +45 \pm 2^\circ$ ; 546

[c = 5 in 6M HCl]) is dissolved in 300 ml 6.8 N methanolic hydrochloric acid and stirred at room temperature for 18 hours. The mixture is concentrated and the residue shaken with 300 ml saturated potassium carbonate solution and 600 ml ether. The aqueous phase is then extracted three times each with 600 ml ether. The combined organic phases are dried over sodium sulphate, filtered, concentrated and dried to a constant weight in a high vacuum to give a clear light yellow oil of the (2S,3R)-L-allo-isoleucine methyl ester. Further methyl ester is 20 obtained by extracting the above mentioned aqueous phase.

-14-

$[\alpha]^{20}_D = 45^\circ$  ( $c = 3$  in  $\text{CH}_2\text{Cl}_2$ ); NMR 100 MHz ( $\text{CDCl}_3$ )

0.81 - 1.01 ppm (6H, 4 Peaks,  $\text{CH}_3\text{-C-3}$ ,  $\text{CH}_3\text{-CH}_2\text{-C-3}$ ),  
3.46 (1H, d,  $J = 4\text{Hz}$ , C-2-H), 3.71 (3H, s,  $\text{COOCH}_3$ ).

ii) Condensation with CBO-L-Proline

- 5 26.15 g (161.5 mM) solid N,N-carbonyldiimidazolyl is added with stirring to 40.35 g (161.5 mM) 2S-carbobenzoxy-L-proline in 600 ml tetrahydrofuran. After 5 minutes the  $\text{CO}_2$  evolution finished. The mixture is light yellow and is stirred for a further 1 hour at room temperature. To this mixture a solution of 22.95 g (158.3 mM) (2S,3R)-L-allo-isoleucine methyl ester in 155 ml tetrahydrofuran is added dropwise.

The mixture is stirred for 2 hours at room temperature, shaken and extracted with 1 litre ether. The organic phase is washed twice with water. The aqueous washings are re-extracted 15 with ether.

The combined organic phases are dried over sodium sulphate, filtered, concentrated and dried in a high vacuum at  $30^\circ$  to give a compound of formula VIII as a clear light yellow oil.

-15-

iii) Removal of the CBO group

A solution of 64 g (170 mM) of the compound of formula VIII in 800 ml ethanol is added as a prehydrogenated mixture of 12 g 10% palladium-on-charcoal catalyst in 500 ml methanol. The mixture is  
5 hydrogenated (room temperature, 757 mm Hg, reaction time 2 1/2 hours) taking up 2.9 litres hydrogen. The reaction mixture is filtered through a filtering aid such as Hyflo (registered Trademark), washed with 1 litre  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  (1 : 1) and dried to give after concentration a compound of formula VII as a yellow oil.

10 vi) Cyclization to diketo piperazine (compound of formula VI)

The compound of formula VII is heated in a high vacuum at 120° for 2 1/2 hours. The resultant partially crystalline mixture is stirred with ether.

Hexane is added forming a crystalline component (8.66 g) and an  
15 oily component (27.4 g). The oily component was then re-subjected to the cyclization reaction.

The crystalline component which is the heading compound is recrystallized from ether/hexane to give colourless needles.  
M.pt. 132-135°;  $[\alpha]^{20} = -156^\circ$  (c = 1 in  $\text{CH}_2\text{Cl}_2$ ).

-16-

NMR 360 MHz (CDCl<sub>3</sub>) 0.80 ppm (3H,d,J = 6,5 Hz, CH<sub>3</sub>-C-9), 0.98 (3H,t,J = 7 Hz, CH<sub>3</sub>-CH<sub>2</sub>-C-9), 1.42 (2H,m), 1.92 (1H,m), 2.45 (2H,m), 2.38 (2H,m), 3.52 bis 3.59 (2H,m), 4.08 (2H,m).

5 b) (2R,5S,11S,12S)-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine-2-carboxylic acid ethyl ester [compound of formula IV]

i) 21 g (100 mM) (3S,8aS)-3-(2R-butyl)-hexahydro-pyrrolo[1,2-a]-piperazine-1,4-dione are mixed with 200 ml absolute dioxane, 57.3 10 ml (334 mM) N-ethyl-N,N-diisopropylamine and 53.32 g (178.6 mM) S-(+)-2-benzyloxy-2-chloroformyl-3-methyl-butyric acid ethyl ester under nitrogen and boiled under reflux for 3 hours. The reaction mixture is cooled and partitioned between 1 litre ether and cold 1N hydrochloric acid. The organic phase is twice washed 15 with saturated potassium bicarbonate solution and the aqueous phase reextracted with ether. The combined organic phases are dried over sodium sulphate, filtered and concentrated to give a yellow oil of the condensed product.

ii) This product is treated with a prehydrogenated mixture of 20 10 g 10% palladium on charcoal catalyst in 2.6 litres absolute ethanol. The mixture is hydrogenated for 18 hours at normal pressure, filtered through a filtering aid such as Hyflo, and evaporated. The residue is dried in a high vacuum to give a yellow oil which is recrystallised from ether/petroleum ether to 25 give the heading compound.

-17-

M.pt. 95-96°;  $[\alpha]^{20} = + 9^\circ$  (c = 1 in ethanol).

c) (2R;5S;11S;12S)-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine-2-carboxylic acid

- 5 172 ml 1N sodium hydroxide are added to 28.64 g of the ester obtained in step b) suspended in 20 ml methanol. The resultant colourless solution is stirred for 19 hours at room temperature, and then washed twice with 500 ml ether. The combined organic washings are back-extracted with water. All the
- 10 aqueous phases are made acid with 103.2 ml 2N hydrochloric acid at 0° and the heading compound falls out of solution as an oil. A crystallizate is obtained after treatment in an ultrasound bath, and is then dried at 50° for 24 hours. The heading compound is in the form of colourless crystals.
- 15 M.pt. 114-115°; second crystalline form: M.pt. 172-173°;  $[\alpha]^{20} = -11.7^\circ$  (c = 1.5 in pyridine).

-18-

d) (2R;5S;11S;12S)-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine-2-carboxylic acid-hydrazide

A solution of 8.37 ml oxalyl chloride in 33 ml methylene chloride is added to a solution of 9.04 ml dimethylformamide in 132 ml methylene chloride at -10° to form a white suspension which is stirred for a further 15 minutes at -10°.

23.36 g (65.8 mM) of the acid obtained in step c) in solid form are added and the temperature of the mixture rises to -6°. The resultant bright yellow solution is stirred for a further 30 minutes at -60°. A solution of 42.9 g sodium azide in 204 ml water is added over 4 minutes. The temperature of the mixture rises to +5° and the mixture becomes reddish. The mixture is stirred for a further 15 minutes at -10°, and extracted with 900 ml methylene chloride. The organic phases are shaken with 420 ml of an ice-cold saturated potassium bicarbonate solution.

The aqueous phase is twice back-extracted with 800 ml methylene chloride. The combined organic phases are dried over sodium sulphate, filtered, concentrated and dried in a high vacuum. The residue is recrystallized from ether/methylene chloride to give colourless crystals.

M.pt. greater than 175° (decomposition).

-19-

e) (2R;5S;11S;12S)-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]-pyrazine-2-carbaminic acid-benzyl-ester

13.52 ml (130.8 mM) absolute benzyl alcohol is added to a  
 5 solution of 16.54 g (43.6 mM) in 110 ml of the acid hydrazide obtained in step d) and boiled under reflux for 35 minutes. The easily vaporized part of the resultant clear yellow solution is distilled off and the surplus benzyl alcohol taken off at 120° in a high vacuum. The resultant crystalline yellow residue is  
 10 purified by stirring in ether and crystallization from methylene chloride/ether.

M.pt. 197 - 199°;  $[\alpha]^{20} = +40^\circ$  (c = 0.6 in methanol).

f) (2R;5S;11S;12S)-2-amino-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine-  
 15 monohydrochloride  
 (compound of formula II)

16 g (34.8 mM) of the carbaminic acid derivative obtained in step e), 8 g of 10% palladium-on-charcoal catalyst, 1.12 litres methanol and 112 mM hydrochloric acid are mixed and hydrogenated  
 20 at 19° under normal pressure. The mixture is filtered. The filtrate is concentrated at 30° until it begins to crystallize, mixed with 500 ml ether and stirred. The crystallizate is filtered off, washed with ether and dried to a constant weight under a high vacuum. M.pt. greater than 145° (decomp.).  
 25  $[\alpha]^{20} = +55^\circ$  (c = 0.15 in dimethylformamide).

The compounds of the invention and their pharmaceutically acceptable acid addition salts thereof, hereinafter referred to as the pharmaceutical compounds of the invention, are new and exhibit pharmacological activity and may therefore be used as pharmaceuticals.

In particular the pharmaceutical compounds of the invention exhibit a prolactin secretion inhibition activity as indicated in standard animal tests. For example, in one test according to the method of E. Flückiger et al., *Experienta* 34, 1330-1332, 1978, the administration subcutaneously of the pharmaceutical compounds of the invention at a dose of from about 0.1 mg/kg to about 10 mg/kg animal body weight inhibit implantation in the rat.

In this test the title compound of example 1 has a ED<sub>50</sub> of about 1.84 mg/kg s.c.. The compound is thus some 5 times more active than co-dergocrine in this test.

The pharmaceutical compounds of the invention are therefore indicated for use as prolactin secretion inhibitors, e.g. for the treatment of lactation, galactorrhea, hyperprolactinaemic hypogonadism, acromegaly, or prolactinoma.

The pharmaceutical compounds of the invention also exhibit serotonergic activity as indicated in standard animal tests. For example, in the sleep/wake cycle test at administration i.p. at from about 0.3 to about 10 mg/kg or p.o. at from about 1 to about 10 mg/kg animal body weight the compounds induce a reduction of the paradoxical sleep phase and a prolongation of the wake phase, in accordance with the principles described in J.M. Vigouret et al., Pharmacology, 16, (Suppl. 1), 1, 156-173 (1978).

The serotonergic activity is confirmed in that the compounds inhibit the reserpine syndrome in the PGO-potential model in implanted cats on administration of from about 0.01 to about 1 mg/kg i.v. in accordance with the above mentioned article of J.M. Vigouret et al.

In this test the example 1 compound had an ID<sub>50</sub> of 0.11 mg/kg i.v. and is thus indicated to be 3 times more active than co-dergocrine in this test.

Moreover the compounds increase the local cerebral glucose utilisation in the sensomotor cortex, e.g. Hippocampus and Nucleus habenula, as indicated by the carbon-14-2-deoxyglucose autoradiographic technique with the rat brain on administration i.p. of from about 0.01 to about 3 mg/kg of the compounds [for method see e.g. L. Solokoff, Journal of Cerebral Blood Flow and Metabolism, 1981, (1), 7-36; H.E. Savaki et al., Brain Research 1982, 233, 347-358 and J. McCulloch et al., Journal of Cerebral Blood Flow and Metabolism 1981, 1, 133-136].

-22-

The pharmaceutical compounds of the invention are thus additionally indicated for use in the treatment of cerebral insufficiency, e.g. for senile dementia, particularly the early forms thereof, and for increasing vigilance.

Furthermore, the pharmaceutical compounds of the invention exhibit sympatholytic  $\alpha$ -blocking activity as indicated in standard tests. For example, in the infusion cat this activity can be shown on administration i.v. of doses from about 0.01 to about 1 mg/kg s.c.. Also in the anaesthetized normotonic dog on administration i.v. from about 0.001 mg/kg to about 10 mg/kg animal body weight an anti-hypertensive effect is seen in accordance with the method of D.Chu., A.Hofmann and E.Stürmer, Naunyn-Schmiedeberg's Arch. Pharmacol. (1975), Suppl. 287, R 18. An anti-hypertensive activity is also observed in the spontaneously hypertensive rat test on administration of from about 0.01 to about 10 mg/kg s.c. of the compound.

In general the compound of Example 1 is on average 1 to 3 times more potent than co-dergocrine in these tests.

The compounds are therefore furthermore indicated for use as anti-hypertensives, especially for geriatrics.

The pharmaceutical compounds of the invention increase the cerebrovascular blood flow, as indicated in standard tests. For example the compounds improve the post-ischemic EEG recovery in the isolated rat head test on administration of from about 0.2 to about 0.4  $\mu\text{g}/\text{min}$  into the carotid artery according to the method of N. Wiernsperger, P.Gygax, O. Hunziker and A. Schweizer, J.Pharmacol. (Paris), 1979, 10, 4 bis, p.489 to 501 at 495, and P.Gygax and N.Wiernsperger Proc. Int.Cerebrovascular diseases SIR (1980) p. 239-254.

The pharmaceutical compounds of the invention are therefore indicated for use in the treatment of stroke.

The compounds of the invention and their pharmaceutically acceptable acid addition salts are therefore indicated for use as  
5 pharmaceuticals, for use as a prolactin secretion inhibitor, for increasing vigilance, for the treatment of senile dementia, hypertension or stroke. The senile dementia or anti-hypertension indication is the preferred indication. The title compound of Example 1 is the preferred compound.

10 For each of the above indications an indicated daily dosage of a compound of the invention or its pharmaceutically acceptable acid addition salts is from about 0.3 to about 30 mg, e.g. 2 to 4 mg, conveniently administered 2 to 4 times a day in divided doses in unit dosage form or in sustained release form.

-24-

In general pharmaceutical compositions of the invention in unit dosage form contain at least 0.01 mg or at least 0.1 mg of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof and at least 0.1% by weight, e.g. up to 90%  
5 by weight, e.g. from 1 to 10% by weight, of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof.

Particularly suitable unit dosage forms for e.g. oral or rectal administration contain from about 0.1 to 15 mg, or  
10 especially from 0.1 to 9 mg, of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof. The unit dosage forms may be in the form of for example tablets, capsules, dragees or suppositories.

Liquid solutions, e.g. drop solutions for oral use may  
15 contain at least 0.1 mg/per ml, e.g. 0.5 mg to 2 mg, per ml.

Particularly suitable unit dosage forms e.g. for parenteral administration, e.g. a sterile injectable suspension, contain from about 0.01 to about 3 mg, or especially from 0.03 to 1 mg of a compound of the invention or a pharmaceutically acceptable acid  
20 addition salt thereof.

The compounds of the invention may if desired be administered in the pharmaceutically acceptable acid addition salt thereof. Such salts exhibit the same order of activity as the compound of the invention as such in free base form. It is  
25 preferred to administer the compound of the invention in the free base form.

The present invention accordingly provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier or diluent. Such  
5 formulations may be made in conventional manner, e.g. as known for other ergot peptide alkaloids, e.g. co-dergocrine.

Thus the compounds of the invention and their pharmaceutically acceptable acid addition salts may be mixed with pharmaceutically acceptable carriers and diluents and if desired  
10 other excipients to produce pharmaceutical compositions for oral, rectal or parenteral administration. Thus tablets, granulates, dispersible powders, dragees, capsules, syrups, suspensions, solutions and elixirs may be produced for oral administration. Suppositories for rectal administration and solutions and  
15 suspensions for parenteral administration may also be produced. Oral pharmaceutical compositions may include one or more excipients, e.g. sweetening agents, aroma, dyestuffs, and conserving agents in order to produce an acceptable and palatable composition.

20 For example, tablets may contain a compound of the invention or a pharmaceutically acceptable acid addition salt thereof admixed with diluents, e.g. calcium carbonate or lactose, dispersing agents, such as starch and alginic acid, binding agents such as starch, polyvinylpyrrolidone or gelatine,  
25 lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be coated using conventional techniques in order to delay the disintegration thereof and retard the resorption in the gastro-intestinal tract in order to produce prolonged activity.

-26-

Capsules may contain an ergot 5S-(2R-butyl) peptide alkaloid or a pharmaceutically acceptable acid addition salt thereof admixed with a solid diluent such as lactose or starch and a lubricant, e.g. magnesium stearate.

- 5        Suspensions, sirups and elixirs may contain an ergot 5'S-(2R-butyl) peptide alkaloid admixed with conventional excipients for such compositions such as suspending agents, e.g. methyl cellulose, tragacanth and sodium alginate, tensioactive agents such as lecithin, polyoxyethylene stearate or
- 10    polyoxyethylene sorbitan monooleate and conserving agents such as ethyl para-hydroxy benzoate.

Injectable compositions, suppositories and other pharmaceutical compositions may indicated as above be produced in conventional manner.

- 15        From the point of view of ease of production and acceptability solid dosage forms are preferred, e.g. tablets or capsules.

Examples of pharmaceutical compositions, which may be produced in conventional manner, are as follows:-

-27-

| <u>Tablets</u>                                                 |               |
|----------------------------------------------------------------|---------------|
| <u>Constituent</u>                                             | <u>Weight</u> |
| Compound of the invention, e.g.<br>title compound of Example 1 | 0.1 mg        |
| 5 Tartaric acid                                                | 0.1 mg        |
| Lactose                                                        | 85.9 mg       |
| Corn starch                                                    | 10 mg         |
| Gelatine                                                       | 0.3 mg        |
| Magnesium stearate                                             | 0.3 mg        |
| 10 Talc                                                        | 2 mg          |

| <u>Capsules</u>                                                     |          |
|---------------------------------------------------------------------|----------|
| Compound of the invention, e.g.<br>title compound of Example 1      | 0.1 mg   |
| Diluents and lubricants (lactose,<br>15 starch, magnesium stearate) | 299.9 mg |

-28-

Liquid-compositions

|                                                                  | WEIGHT (mg)                                          |                                         |
|------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------|
|                                                                  | <u>sterile injectable</u><br><u>suspension</u> ..... | <u>oral liquid</u><br><u>suspension</u> |
| 5 Compound of the invention, e.g.<br>title compound of Example 1 | 0.05                                                 | 0.1                                     |
| Sodium carboxymethyl<br>cellulose USP                            | 1.25                                                 | 12.5                                    |
| Methylcellulose                                                  | 0.4                                                  | --                                      |
| 10 Polyvinylpyrrolidone                                          | 5                                                    | --                                      |
| Lecithin                                                         | 3                                                    | --                                      |
| Benzyl alcohol                                                   | 0.01                                                 | --                                      |
| Magnesium aluminium silicate                                     | --                                                   | 47.5                                    |
| Aroma                                                            | --                                                   | q.s.                                    |
| 15 Dyestuff                                                      | --                                                   | q.s.                                    |

-29-

|                                                                  | Weight (mg)                                         |                                           |
|------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------|
|                                                                  | <u>Sterile injectable</u><br><u>suspension.....</u> | <u>Oral liquid</u><br><u>suspension..</u> |
| Methylparaben, USP                                               | --                                                  | 4.5                                       |
| 5 Propylparaben, USP                                             | --                                                  | 1.0                                       |
| Polysorbate 80 [e.g.<br>Tween 80 (registered<br>Trademark)], USP | --                                                  | 5                                         |
| Sorbitol solution, 70%, USP                                      | --                                                  | 2,500                                     |
| Stabilizing buffer                                               | q.s.                                                | q.s.                                      |
| 10 Water                                                         | q.s. to 1 ml                                        | q.s. to 5 ml                              |

The above composition may be administered, e.g. once daily,  
for the treatment of senile dementia.

-30-

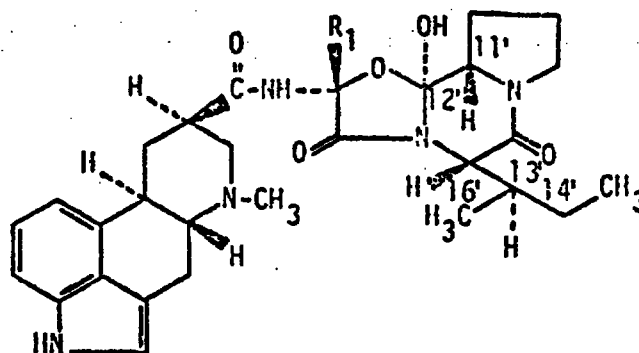
The compounds of the invention or their pharmaceutical acceptable acid addition salts may be administered from about 1 to 30 mg/kg animal body weight daily over 4 weeks to dogs and show a good general tolerability. For example, the title compound 5 of example 1 shows very slight ergot specific side effects up to 10 mg/kg animal body weight p.o. over 4 weeks, e.g. only slight emesis, salivation, loss of weight, and reduction in feed uptake.

At 30 mg/kg animal body weight p.o. no significant cardiotoxic effects are observed. Thus the title compound of 10 Example 1 is indicated to be well tolerated, even better than co-dergocrine.



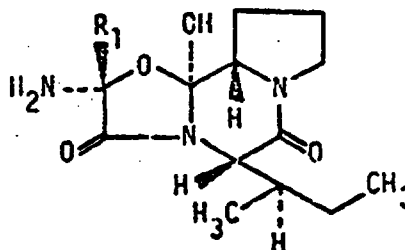
## CLAIMS

1. A process for the preparation of an ergot 5'S-(2R-butyl) peptide alkaloid or an acid addition salt thereof which includes the step of condensing an acid addition salt of a corresponding
- 5 5'S-sec-(2 R-butyl) aminocyclol with a reactive acid derivative of a corresponding lysergic acid derivative and recovering the resultant above-mentioned compound as such or as an acid addition salt thereof.
- 10 2. A process for the production of a compound of formula I of claim 1



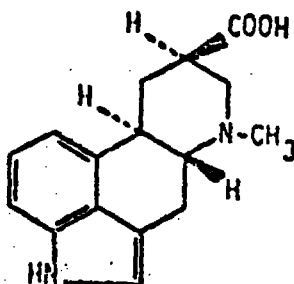
wherein  $R_1$  is methyl, ethyl or isopropyl,  
or an acid addition salt thereof,

- 15 compound of formula II



wherein  $R_1$  is as defined above,

with a reactive acid derivative of a compound of formula III



III

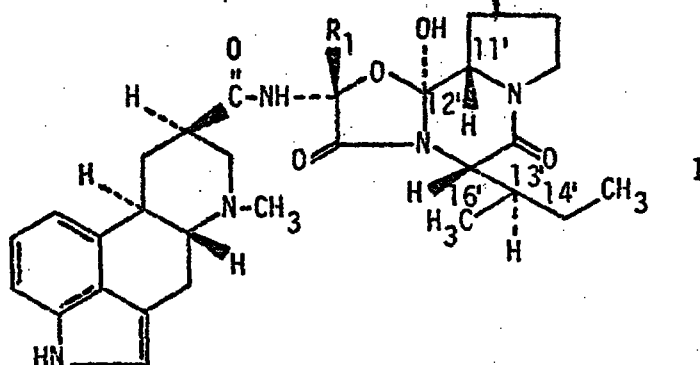
3. A process for the production of an ergot 5<sup>8</sup>-(2R-butyl) peptide  
5 alkaloid or an acid addition salt thereof substantially as  
hereinbefore described with reference to Example 1.

4. An ergot 5'S-(2R-butyl) peptide alkaloid or an acid addition salt thereof whenever produced by a process as claimed in claim 1,2 or 3.

10 5. An ergot 5'S-(2R-butyl) peptide alkaloid and its addition salts.



6. A compound of claim 5 of formula I



wherein  $R_1$  is methyl, ethyl or isopropyl, and its acid addition salts.

7. A compound of claim 5 or 6 or an acid addition salt thereof, in admixture with less than 5% by weight of the corresponding 5'S-(2S-butyl) epimer.

8. A compound of claim 5 or 6 or an acid addition salt thereof, in admixture with less than 1% by weight of the corresponding 5'S-(2S-butyl) epimer.

9. (5R,8R,10R)-N-[(2R,5S,11S,12S)-5-(2R-butyl)-octahydro-12-hydroxy-2-isopropyl-3,6-dioxo-8H-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazinyl]-6-methyl-ergoline-8-carboxylic acid amide and its acid addition salts.



-34-

10. A compound of claim 9 or an acid addition salt thereof in admixture with less than 5% by weight of dihydro- $\beta$ -ergocryptine, or an acid addition salt thereof.
- 5 11. A compound of claim 9 or an acid addition salt thereof in admixture with less than 1% by weight of dihydro- $\beta$ -ergocryptine or an acid addition salt thereof.
12. A compound according to any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical.
- 10 13. A compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof, for use as a prolactin secretion inhibitor, for increasing vigilance, or for the treatment of senile dementia, hypertension or stroke.
- 15 14. A pharmaceutical composition comprising a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier or diluent.



-35-

15. A pharmaceutical composition as claimed in claim 14 in unit dosage form containing at least 0.01 mg of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.
- 5 16. A pharmaceutical composition as claimed in claim 15 containing from 0.1 to 15 mg of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.
- 10 17. A pharmaceutical composition as claimed in claim 16 for oral or rectal use containing from 0.1 to 9 mg of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.
- 15 18. A pharmaceutical composition as claimed in claim 15 for parenteral use containing from 0.01 to 3 mg of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.
19. A pharmaceutical composition as claimed in claim 15 for parenteral use containing from 0.03 to 1 mg of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.
- 20



-36-

20. A pharmaceutical composition in solution form containing at least 0.1 mg per ml of a compound as claimed in any one of claims 4 to 11 or a pharmaceutically acceptable acid addition salt thereof.

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