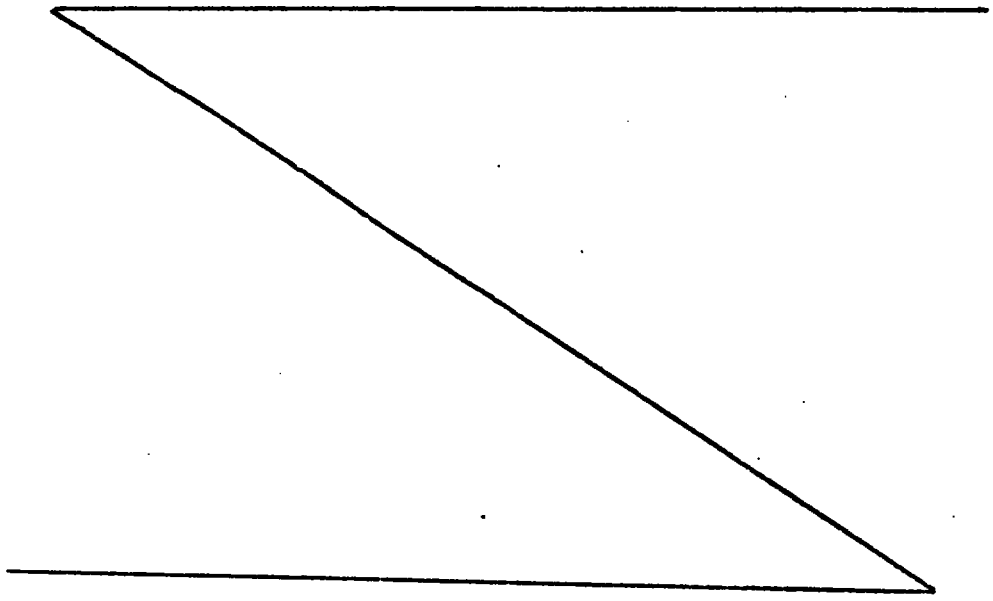
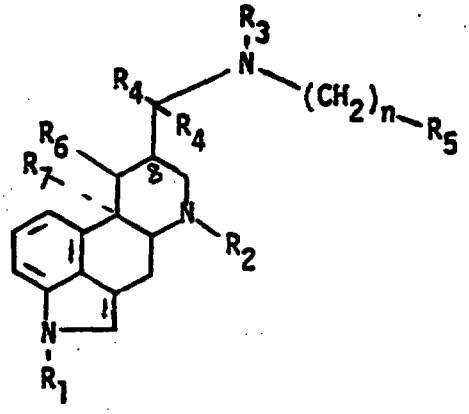
(11) 2108502

N-Substituted ergoline- and 9,10-didehydro-ergoline-8-carboxamide- and -8-aminomethyl-derivatives, their production and their pharmaceutical composition.

The invention relates to novel N-substituted ergoline- and 9,10-didehydro-ergoline-8-carboxamide- and -8-aminomethyl-derivatives, their production and their pharmaceutical compositions.

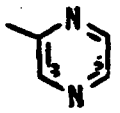


The present invention provides compounds of formula I



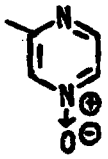
I

wherein R_1 is (C_{1-4})alkyl, or H or a precursor thereof,
R_2 is H or (C_{1-6})alkyl
R_3 is H or (C_{1-4})alkyl
the two R_4's both are H or together are an oxo group
R_5 is the radical



which is unsubstituted or substituted with one or two halogen atoms, (C_{1-4})alkyl or -alkoxy groups or with one hydroxy group in position 3 or 5 or

is the radical



which is unsubstituted or substituted by one or two halogen atoms

R_6 and R_7 both are H or together are a bond and
n is 0, 1 or 2,

hereinafter referred to as compounds of the invention.

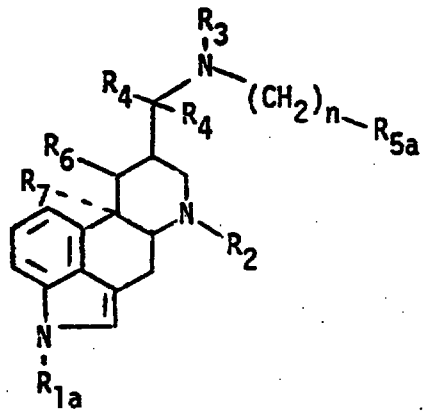
The configuration of the side chain in position 8 is either α or β.

As precursors in position 1 are meant such substituents which under physiological conditions may be converted into H. Such substituents are e.g. $-CH_2OH$ or (C_{1-4})alkoxymethyl, especially CH_3OCH_2-. Halogen atoms are F, Cl, Br or I, preferably Cl or Br, especially Cl.

Preferred substituents in the compounds of formula I are individually:
R_1 = H, (C_{1-4})alkyl or (C_{1-4})alkoxymethyl, especially H, methyl or methoxymethyl, particularly H; R_2 = (C_{1-4})alkyl, especially methyl or ethyl, particularly methyl; R_3 = H or methyl, particularly H; both R_4 are together = oxo; R_5 = unsubstituted 2-pyrazinyl, 4-oxido-2-pyrazinyl or 1H-2-oxo-pyrazin-3-yl, especially unsubstituted 2-pyrazinyl; n = 0 or 1 , especially 0; R_6 and R_7 each are H; the configuration of the side chain in position 8 is especially β. Preferred compounds are such in which R_1 = H; R_2 = (C_{1-6})alkyl, R_3 = H, both R_4's together are oxo, R_5 = unsubstituted 2-pyrazinyl, n = 0, R_6 and R_7 each are H, and the configuration of the side chain in position 8 is β.

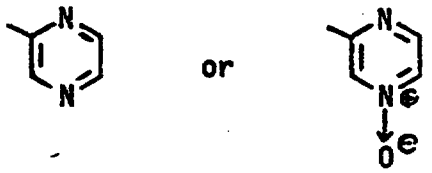
(14)

A group of compounds comprises the compounds of formula Ia



Ia

wherein R_{1a} is H or methyl
R_2 is H or (C_{1-6})alkyl
R_3 is H or (C_{1-4})alkyl
the two R_4's each represent H or together represent an oxo group
R_{5a} is the radical

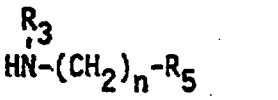


which are unsubstituted or are substituted by 1 or 2 halogen atoms
R_6 and R_7 both are H or together are a bond and
n is 0 or 1.

The present invention in another aspect provides a process for

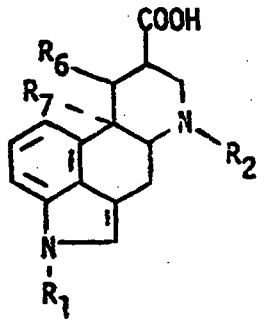
the production of a compound of the invention, which includes the step of

a) acylating a compound of formula II



II

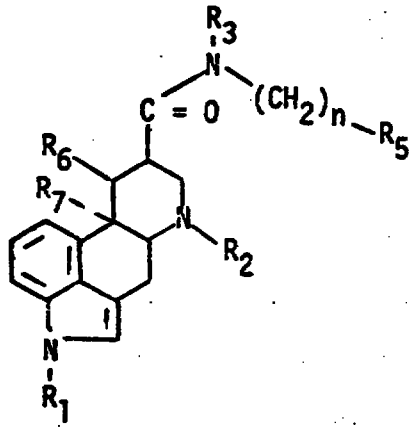
wherein R_3, R_5 and n are as defined above with a compound of formula III



III

wherein R_1, R_2, R_6 and R_7 are as defined above or with a reactive functional acid derivative thereof, to produce a compound of formula I wherein the two R_4's together represent an oxo group,

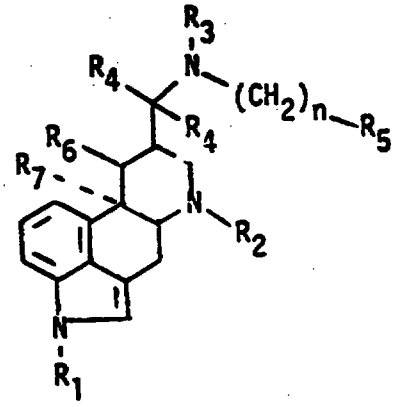
b) reducing a compound of formula Ib



Ib

wherein R_1 to R_3 and R_5 to R_7 and n are as defined above to produce a compound of formula I wherein the two R_4's each represent H, or

c) alkylating a compound of formula Ic



Ic

wherein R_1 to R_7 and n are as defined above with the proviso that at least one of R_1 to R_3 is hydrogen,
to produce the corresponding compound wherein at least one of R_1 to R_3 is chosen, for R_1, from (C_{1-4})alkyl or an appropriate precursor of H, for R_2, from (C_{1-6})alkyl and/or, for R_3, from (C_{1-4})alkyl.

In process a) the starting materials of formula II and III are known - e.g. compounds II from Gazz.Chim.Ital.91, 1431 (1961) and 93,339 (1963) and from J.Org. Chem. 38,2049 (1973), or they may be produced from known compounds using known methods. Conventional ergoline amide synthesis reactions may be used, preferably using reactive functional acid derivative of a compound of formula III. Thus, the starting materials of formula III may preferably be amidated in known manner by an active ester, e.g. by means of a reaction with oxalyl chloride and dimethylformamide in the presence of pyridine in a suitable solvent e.g. acetonitrile, with a pyrazine of formula II containing an aminogroup e.g. as described in the Swiss Patent Specification No. 588.486.

In process b) the oxo group in the amides of formula Ib may be reduced by known methods, e.g. in an inert solvent, using a complex metal hydride, e.g. lithium aluminium hydride.

In process c) the alkylation may be effected in conventional manner, using appropriate alkylating agents to alkylate the appropriate group.

The term alkylation includes not only the introduction of an unsubstituted alkyl radical but also the introduction of $-CH_2OH$ and (C_{1-4})-alkoxymethyl. Where selective alkylation is required, it may be desirable to block temporarily other reactive groups present. Introduction of the CH_2OH radical in position 1 may be effected with formaldehyde. The CH_2OH radical may be subsequently etherified with an alkanol, e.g. methanol, under acidic conditions.

Introduction of an alkyl group R_3 in the side chain may be effected by an alkylation agent in the presence of a base, e.g. sodium hydride, in tetrahydrofuran.

However, instead of introduction an alkyl group R_3 as a final reaction step, process a) is preferred starting from a compound of formula II in which R_3 is the appropriate alkyl group.

Introduction of an alkyl group R_2 in position 6 may be effected by reductive alkylation, e.g. in case of a methyl group by reaction with formaldehyde and $NaBH_4$, or, generally by an alkyl halide in the presence of a base, e.g. K_2CO_3.

The compounds of formula I may be recovered in, for example, free base form or acid addition salt form.

Mixtures of 8α and 8β ergolines may result. These may be separated in conventional manner, e.g. by thin layer chromatography or crystallization. The two isomers may be distinguished by conventional spectroscopic means, e.g. n.m.r. spectroscopy as indicated hereinafter in Example 11.

Starting materials if unknown may be prepared in analogous manner to similar known compounds or in analogous manner to that described herein.

The acid addition salt forms of a compound of formula I may be produced in conventional manner from the free base forms and vice versa. Suitable acids include hydrochloric acid, methanesulphonic acid, fumaric acid, tartaric acid or maleic acid.

In the following Examples all temperatures are in degrees centigrade and are uncorrected.

EXAMPLE 1 : 6-methyl-N-pyrazinylergoline-8β-carboxamide

850 ml of dimethyl formamide and 700 ml of acetonitrile are placed in a three-necked flask at -20° in a nitrogen atmosphere. A solution of 98 g of oxalyl chloride in 200 ml of acetonitrile is added in drops at the same temperature with vigorous stirring, over the course of 25 minutes. The reaction mixture is stirred for a further 15 minutes at -20°, and then 189 g of 6-methylergoline-8β-carboxylic acid are added. The greyish-green suspension is stirred for one hour at 0°, then a solution of 86.5 g of aminopyrazine in 500 ml of pyridine is added to the reaction mixture which has been cooled to -35°. After stirring for three hours at 0°, the reaction mixture is poured onto 2N soda solution and extracted with methylene chloride. The crude product which is obtained by evaporating the solvent is purified by crystallisation from ethyl acetate.
M.p.: 223-224° $[\alpha]_D^{20}$ = - 122.1° (c = 1.89 in DMF).

hydrochloride (from methanol), m.p.: 225° (decomp.)
$[\alpha]_D^{20}$ = - 100.1° (c = 1.62 in DMF).

hydrogen fumarate (from methanol), m.p.: 245-248° (decomp.)
L(+)-tartrate (from methanol), m.p.: 215-225° (decomp.)
methane sulphonate (from methanol), m.p.: 258-261° (decomp.)
hydrogen maleinate (from methanol), m.p.: 151-153° (decomp.)

EXAMPLE 2 : 6-ethyl-N-pyrazinylergoline-8β-carboxamide

In an analogous manner to that described in the foregoing Example, the crude 6-ethyl-N-pyrazinylergoline-8β-carboxamide is prepared from 6-ethylergoline-8β-carboxylic acid (obtainable by ethylation of the corresponding 6-nor compound in accordance with Helv. Chim. Acta, 53, 2197-2201 (1970))

as a starting product. The crude product is purified by chromatography on a column of silica gel. The product, which is obtained using 6% methanol in methylene chloride as the eluant, is crystallised from methylene chloride / n-hexane.

M.p.: 151-155°, (decomp.)

$[\alpha]_D^{20}$ = - 109.2° (c = 1.63 in DMF).

EXAMPLE 3 : 1,6-Dimethyl-N-pyrazinylergoline-8β-carboxamide

In an analogous manner to that described in Example 2 for 6-ethyl-N-pyrazinylergoline -8β-carboxamide, the title compound is prepared from 1,6-dimethylergoline-8β-carboxylic acid [prepared from 6-methylergoline-8β-carboxylic acid ethylester, in accordance with the process described in Helv. Chim. Acta 40, 1721 (1957)] as a starting compound. The product is obtained by crystallisation from acetone. Decomposition without melting above 200°.

$[\alpha]_D^{20}$ = -57.3° (c = 0.66 in pyridine)

EXAMPLE 4 : 1-Methoxymethyl-6-methyl-N-pyrazinylergoline-8β-carboxamide

4 g of 6-Methyl-N-pyrazinylergoline-8β-carboxamide (see Example 1) dissolved in 42 ml of acetic acid are placed in a three-necked bottle and diluted with 200 ml of water. 42 ml of an aqueous formaldehyde solution (35% of weight) are added. The mixture is stirred for three hours at 60-70°, cooled to 20°, adjusted to a pH-value of 8 with a 5N sodium hydroxide solution and extracted with methylene chloride. After evaporation of the solvent, 3,28 g of the obtained crude product, 1-hydroxymethyl-6-methyl-N-pyrazinylergoline-8β-carboxamide, are dissolved in 270 ml of absolute methanol after which

52 g tartaric acid is added and the mixture is stirred for three hours at 60°. The solvent is evaporated in vacuo. The residue is taken up in water, neutralized with a 2N potassiumbicarbonate solution and extracted with methylene chloride. The crude product, obtained after evaporation of the solvent, is purified by chromatography on a column of silica gel. The product is eluted with 3% methanol in methylene chloride and is dissolved in acetone.Two equivalents of tartaric acid are added to form the tartaric acid addition salt.
Decomposition without melting of the crystalline salt above 140°.
$[\alpha]_D^{20}$ = - 57,1° (c = 0,565 in ethanol).

EXAMPLE 5 : 6-Methyl-N-(4-oxido-2-pyrazinyl)ergoline-8ß-carboxamide

In an analogous manner to that described in Example 1, 6-methyl-N-(4-oxido-2-pyrazinyl)ergoline-8ß-carboxamide is prepared from 2-aminopyrazine-4-oxide (prepared according to Gazz. Chim. Ital. 93, 339 (1963)) as a starting compound. After pouring onto a 2N-soda solution and extracting with a mixture of methylene chloride and ethanol (85:15) and evaporating the solvent, the crude product is purified by chromatography on a column of silica gel. The product which is obtained by using 10% methanol in methylene chloride as the eluant, is crystallised from methanol.
Decomposition without melting above 220°.
$[\alpha]_D^{20}$ = - 73,8° (c = 0,6 in dimethylformamide).

EXAMPLE 6 : 6,N-Dimethyl-N-pyrazinylergoline-8ß-carboxamide

In an analogous manner to that described in Example 1, 6-N-

dimethyl-N-pyrazinylergoline-8β-carboxamide is prepared from methylaminopyrazine (obtained according to J.Chem.Soc. (1960) 242) as a starting compound.

After pouring onto a 2N-sodiumbicarbonate solution and extracting with a mixture of methylene chloride and ethanol (9:1) and evaporating the solvent, the crude product is purified by chromatography on a column of silica gel. The product which is obtained by using 9% methanol in methylene chloride as the eluant, is dissolved in ethanol and is treated with an equivalent quantity of 4N hydrochloric acid.

The obtained hydrochloric acid addition salt decomposes without melting above 256°.

$[\alpha]_D^{20}$ = -54.1° (c = 1 dimethylformamide).

EXAMPLE 7: 6-Methyl-N-(2-pyrazinylmethyl)ergoline-8β-carboxamide

In an analogous manner to that described in Example 1, 6-methyl-N-(2-pyrazinylmethyl)ergoline-8β-carboxamide is prepared from aminomethylpyrazine (obtained according to J.Org.Chemistry 38, 2049 (1973)) as a starting compound.

After pouring onto a 2N-soda solution and extracting with methylene chloride and evaporating the solvent, the crude product is purified by chromatography on a column of silica gel using methylene chloride/methanol/concentrated ammonia (93:7:0.7) as the eluant. The pure product is crystallised from ethanol / n-hexane.

Decomposition without melting above 194°.

$[\alpha]_D^{20}$ = -93.0° (c = 1,0 in dimethylformamide).

EXAMPLE 8: 6-Methyl-N-(1H-2-oxopyrazin-3-yl)ergoline-8β-carboxamide

In an analogous manner to that, described in Example 1, 6-methyl-N-(1H-2-oxopyrazin-3-yl)ergoline-8β-carboxamide is prepared from 3-amino-1H-2-oxopyrazine (obtained according to J.Am.Chem.Soc. 78, 242 (1956)) as a starting compound.

The reaction mixture is poured onto a 2N soda solution, saturated with sodium chloride and filtered.

The residue is purified by chromatography on a column of silica gel. The product, which is obtained by using 20% methanol in methylene chloride as an eluant, is dissolved in methanol and is treated with an equivalent quantity of methane-sulphonic acid. The obtained crystalline methane sulphonate salt decomposes without melting above 220°.

$[\alpha]_D^{20}$ = -90.6° (c = 0.5 in dimethylformamide).

EXAMPLE 9: N-(5-Bromopyrazin-2-yl)-6-methylergoline-8β-carboxamide

In an analogous manner to that described in Example 1, N-(5-bromopyrazin-2-yl)-6-methylergoline-8β-carboxamide is prepared from 2-amino-5-bromopyrazine (obtained according to J.Heterocyclic Chemistry 19, 653 (1982)) as a starting compound.

After pouring onto a 2N soda solution and extracting with a mixture of methylene chloride and ethanol (9:1) and evaporating the solvent, the crude product is purified by chromatography on a column of silica gel. The compound is eluted with a mixture of methylene chloride/methanol / concentrated ammonia (97:3:0.3), dissolved in ethanol and treated with an equivalent quantity of 4N hydrochloric acid.

The obtained hydrochloric acid addition salt decomposes without melting above 235°.

$[\alpha]_D^{20}$ = -74.6° (c = 1.0 in dimethylformamide).

EXAMPLE 10: 6-Methyl-N-pyrazinylergoline-8β-methanamine

400 ml of tetrahydrofuran and 8.73 g of Lithiumaluminiumhydride are placed in a three-necked bottle in a nitrogen atmosphere. To the suspension, cooled to -5°, a solution of 10 g 6-methyl-N-pyrazinylergoline-8β-carboxamide in 200 ml of tetrahydrofuran is added dropwise.

The green-yellowish suspension is stirred for 31/2 hours at 0°, after which 60 ml of water / tetrahydrofuran (1:1) are added. After stirring for 11/2 hours at room temperature the mixture is filtered. The crude product, obtained by evaporation of the filtrate, is purified by chromatography on a column of silica gel.

The product obtained by using 15% methanol in methylene chloride as an eluant is crystallised from methanol.

Decomposition without melting above 245°.

$[\alpha]_D^{20} = -96.9°$ (c = 1.0 in dimethylformamide).

EXAMPLE 11: 9,10-Didehydro-6-methyl-N-pyrazinylergoline-8α-carboxamide and 9,10-Didehydro-6-methyl-N-pyrazinylergoline-8β-carboxamide

18.8 g 9,10-Didehydro-6-methylergoline-8β-carboxylic acid in 210 ml of acetonitrileare placed in a three-necked bottle at -20° in a nitrogen atmosphere.

A mixture of 8 g of trifluoroacetic acid and 14.7 g trifluoroacetic anhydride in 40 ml of acetonitrile is added within 2 minutes at the same temperature.

The brownish reaction mixture is stirred for 15 minutes at -20°.

At the same temperature, a mixture of 4.75 g aminopyrazine in 75 ml pyridine is added.

The mixture is warmed up to 0° within 15 minutes and is stirred for 4 1/2 hours.

The reaction mixture is poured onto 2N soda solution and extracted with methylene chloride. The crude product, obtained after evaporation of the solvent, is purified by chromatography on a column of silica gel.

The foam, which is obtained by using 2% methanol in methylene chloride as an eluant, shows in the proton resonance spectrum a mixture of isomeric 8-carboxamides in a weight proportion 8α: 8β = 9:1.

In the proton resonance spectrum both components show a distinct position and multiplicity of their vinylic protons in position 9 of the formulae.

In 9,10-didehydro-6-methyl-N-pyrazinyl-ergoline-8α-carboxamide the signal of this proton is a doublet at 6,59 ppm ($CDCl_3$, relatively to tetramethylsilane) with a vicinal coupling constant value of 5,5 Hz under the same conditions. The same proton of the 8β-isomeric component shows a signal of a broad singlet at 6,45 ppm.

The compounds of the invention exhibit pharmacological activity and are therefore of use as pharmaceuticals, i.e. for therapy.

In particular they have a vasoconstrictor activity which can be demonstrated in vitro on spiral strips of the canine external carotid artery (E.Müller-Schweinitzer Naunyn-Schmiedebergs Arch. Pharmacol.292, 113-118, 1976) in concentration of from 10^{-8} to 10^{-5} Mol/liter.

Moreover, the compounds of the invention exhibit a dose-dependent reduction of the arteriovenous shunt blood flow in the carotid area of cats and dogs.

In one test the reduction of arteriovenously shunted blood flow is observed in the carotid area in cats under chloralose/urethane anesthesia, measured after administration of the active substance and after injection of microspheres (method described by R.P.Hof et al, in Basic Res. Cardiol. 75, (1980), 747-756) into the carotid artery.

A significant reduction is observed on i.v. administration of 10 to 600 µg/kg animal body weight of the compounds.

In a second test the reduction in arteriovenous shunting is observed by an increase in the arteriovenous O_2 saturation difference between the carotid artery and jugular vein in the carotid area in the normotensive anaesthetized dog.

An increase is observed on administration i.v. of from about 20 to about 2000 µg/kg animal body weight of the compounds.

The compounds are therefore indicated for use in the treatment of vascular headaches. Vascular headaches that may be treated include migraine and cluster headaches. The compounds may be administered

to treat headaches already present, i.e. acute therapy or to prevent the occurence of headaches, i.e. interval therapy.

An indicated daily dosage is in the range from about 1 to about 10 mg per os or from about 1 to about 10 mg sublingually for interval therapy, conveniently administered in divided doses 2 to 3 times a day or in sustained release form and from about 0.5 to about 5 mg sublingually for acute therapy, admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of the invention additionally lead to a selective increase in the tonus of the venous system as indicated in the known Mellander test with cats upon administration of from about 5 to about 45 µg/kg i.v. animal body weight.

On the other hand, the resistant vessels constrict only moderately and for a short time.

The compounds are therefore indicated for use in the treatment of orthostatic hypotension.

An indicated daily dosage is in the range from about 5 to about 20 mg of the compounds, admixed with a solid or liquid pharmaceutical carrier or diluent and conveniently administered in divided doses 2 to 3 times a day or in sustained release form.

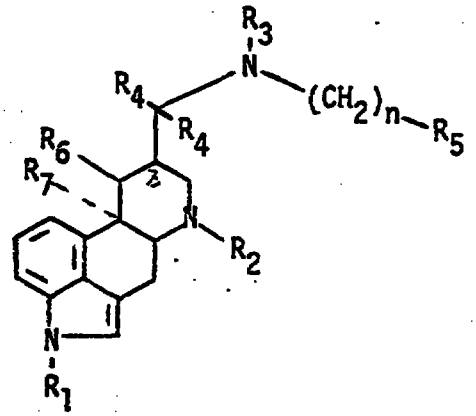
The compound of Example 1 is particularly interesting.
A compound of formula I may be administered in free base or in pharmaceutically acceptable acid addition salt form. Such salt forms exhibit the same order of activity as the free base forms.

The present invention also provides a pharmaceutical composition comprising a compound of the invention in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

Such compositions may be prepared by conventional techniques to be in conventional forms, for example, capsules or tablets.

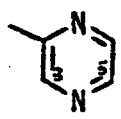
CLAIMS.

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



I

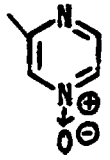
wherein R_1 is (C_{1-4})alkyl, or H or a precursor thereof,
R_2 is H or (C_{1-6})alkyl
R_3 is H or (C_{1-4})alkyl
the two R_4's both are H or together are an oxo group
R_5 is the radical



which is unsubstituted or substituted with one or two halogen atoms, (C_{1-4})alkyl or -alkoxy groups or with one hydroxy group in position

3 or 5 or

is the radical



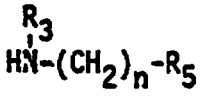
which is unsubstituted or substituted by one or two halogen atoms

R_6 and R_7 both are H or together are a bond and

n is 0, 1 or 2

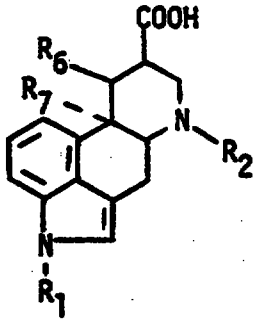
which includes the step of

a) acylating a compound of formula II



II

wherein R_3, R_5 and n are as defined above with a compound of formula III

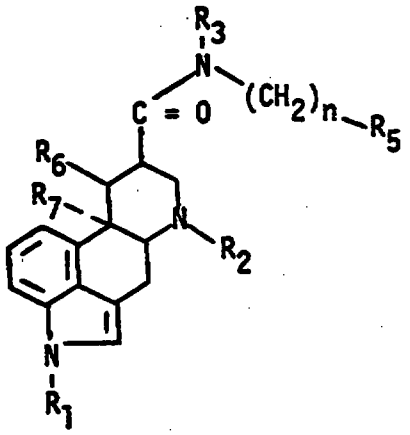


III

* C L M S *

wherein R_1, R_2, R_6 and R_7 are as defined above or with a reactive functional acid derivative thereof, to produce a compound of formula I wherein the two R_4's together represent an oxo group.

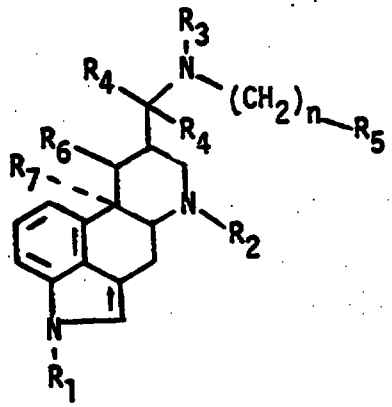
b) reducing a compound of formula Ib



Ib

wherein R_1 to R_3 and R_5 to R_7 and n are as defined above to produce a compound of formula I wherein the two R_4's each represent H, or

c) alkylating a compound of formula Ic



Ic

wherein R_1 to R_7 and n are as defined above with the proviso that at least one of R_1 to R_3 is hydrogen, to produce the corresponding compound wherein at least one of R_1 to R_3 is chosen, for R_1, from (C_{1-4})alkyl or an appropriate precursor of H, for R_2, from (C_{1-6})alkyl - - — — — — — — — —

* C L M S *

and/or, for R_3, from (C_{1-4})alkyl.

2. A process for the production of a compound of formula I defined in claim 1 as hereinbefore described with reference to any one of the Examples.

3. A compound of formula I whenever produced by a process of claim 1 or 2.

4. A compound of formula I as defined in claim 1.

5. A compound of claim 4, wherein R_1 is H, (C_{1-4})Alkyl, $-CH_2OH$ or (C_{1-4})alkoxymethyl.

6. A compound of claim 4, wherein R_1 is H, (C_{1-4})alkyl or (C_{1-4})alkoxymethyl.

7. A compound of claim 4, wherein R_1 is H, methyl or methoxymethyl.

8. A compound of claim 4, wherein R_2 is (C_{1-4})alkyl.

9. A compound of claim 4, wherein R_2 is methyl or ethyl.

10. A compound of claim 4, wherein R_3 is H or methyl.

11. A compound of claim 4, wherein both R_4 together are oxo.

12. A compound of claim 4, wherein each R_4 is H.

13. A compound of claim 4, wherein R_5 is unsubstituted 2-pyrazinyl.

14. A compound of claim 4, wherein R_5 is 4-oxido-2-pyrazinyl.

* C L M S *

15. A compound of claim 4, wherein R_5 is 1H-2-oxopyrazin-3-yl.

16. A compound of claim 4, wherein n is 0.

17. A compound of claim 4, wherein n is 1.

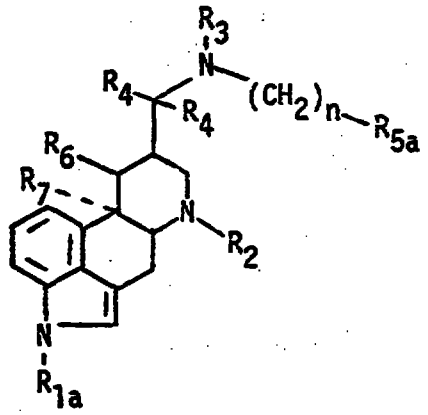
18. A compound of claim 4, wherein R_6 and R_7 each are H.

19. A compound of claim 4, wherein R_6 and R_7 both together are a bond.

20. A compound of claim 4, wherein the configuration of the side chain in position 8 is β.

21. A compound of claim 4, wherein R_1 is H, R_2 is (C_{1-6})alkyl, R_3 is H, both R_4's together are oxo, R_5 is unsubstituted 2-pyrazinyl, n is 0, R_6 and R_7 each are H and the configuration of the side chain in position 8 is β.

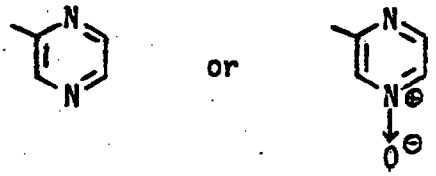
22. A compound of claim 4 of formula Ia



Ia

wherein R_{1a} is H or methyl

R_2 is H or (C_{1-6})alkyl
R_3 is H or (C_{1-4})alkyl
the two R_4's each represent H or together represent an oxo group
R_{5a} is the radical



which are unsubstituted or are substituted by 1 or 2 halogen atoms
R_6 and R_7 both are H or together are a bond and
n is 0 or 1.

23. 6-Methyl-N-pyrazinylergoline-8β-carboxamide.

24. 6-Ethyl-N-pyrazinylergoline-8β-carboxamide.

25. 1,6-Dimethyl-N-pyrazinylergoline-8β-carboxamide.

26. 1-Methoxymethyl-6-methyl-N-pyrazinylergoline-8β-carboxamide.

27. 6-Methyl-N-(4-oxido-2-pyrazinyl)ergoline-8β-carboxamide.

28. 6,N-Dimethyl-N-pyrazinylergoline-8β-carboxamide.

29. 6-Methyl-N-(2-pyrazinylmethyl)ergoline-8β-carboxamide.

30. 6-Methyl-N-(1H-2-oxopyrazin-3-yl)ergoline-8β-carboxamide.

31. 6-Methyl-N-pyrazinylergoline-8β-methanamine.

* C L M S *

32. The mixture of 9,10-didehydro-6-methyl-N-pyrazinylergoline-8β-carboxamide and 9,10-didehydro-6-methyl-N-pyrazinylergoline-8α-carboxamide.

33. A compound of any one of claims 3 to 32 in free base form.

34. A compound of any one of claims 3 to 32 in acid addition salt form.

35. A compound of any one of claims 3 to 32 in free base form or in pharmaceutically acceptable acid addition salt form for use as a pharmaceutical.

36. A compound of any one of claims 3 to 32 in free base form or in pharmaceutically acceptable acid addition salt form for use in the treatment of migraine or of orthostatic hypotension.

37. A pharmaceutical composition which comprises a compound of any one of claims 3 to 32 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.
