

NOVEL 8 α -ACYLAMINOERGOLINES

The present invention relates to novel 8 α -acylamino-ergolines, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.

The 8 α -ergolines comprises a major class of compounds possessing varying degrees and type of biological activity and potential therapeutic utility. Thus DOS 25 30 577 and 26 56 344 disclose a wide range of ergoline derivatives which are variously 8 α -substituted. Amongst possible 8 α -substituents embraced there are included numerous derivatised amino groupings including inter al. acylamino and related residues. The subject compounds are variously described as possessing dopaminergic and prolactin secretion inhibiting activity.

The present invention provides a novel group of 8 α -acylamino ergolines, which have been found to possess especially interesting or advantageous biological activity or profile.

More particularly the present invention relates to compounds of formula I



R₁ is hydrogen or C₁₋₄alkyl,

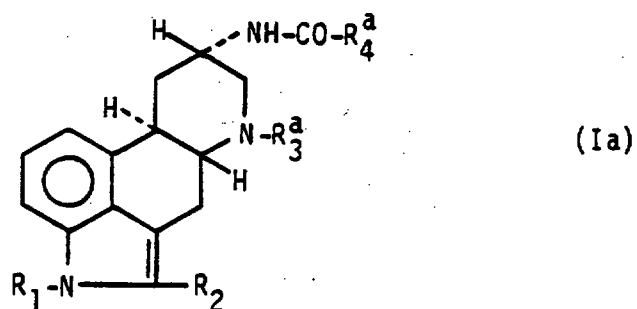
R₂ is hydrogen, chlorine, bromine or methyl.

R₃ is C₁-5alkyl or C₃-5alkenyl in which the double bond is not at the carbon atom adjacent to the nitrogen atom, and

R₄ is C₃-7alkyl; C₃-7cycloalkyl; adamantyl; phenyl; phenyl substituted by one or more members selected from the group consisting of C₁-3alkyl, C₁-3alkoxy, C₁-3alkylthio, trifluoromethyl, hydroxy, nitro, amino and mono- and di-(C₁-3-alkyl)-amino; or phenyl bearing a condensed, non-aromatic, heterocyclic ring having 5- or 6-ring members including 1 or 2 hetero atoms selected from the group consisting of oxygen and sulphur.

with the proviso that when R₁ and R₂ are both hydrogen and R₃ is methyl, R₄ is other than t.butyl, as well as the acid addition salts thereof.

A preferred group of compounds of formula I are those of formula Ia



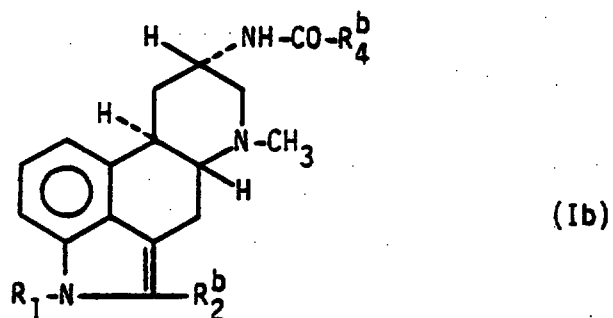
wherein

R_1 and R_2 have the meanings given for formula I,

R_3^a is C₂-5alkyl or C₃-5alkenyl in which the double bond is not at the carbon atom adjacent to the nitrogen atom, and

R_4^a is (i) C₃-7alkyl or C₃-7cycloalkyl; or (ii) phenyl; phenyl substituted by one or two members selected from the group consisting of C₁-2alkyl, C₁-2alkoxy, C₁-2alkylthio, hydroxy and nitro; or phenyl substituted at two adjacent carbon atoms by a divalent residue of formula -O-CH₂-O- or -Z-(CH₂)_n-, wherein Z is oxygen or sulphur and n is 2 or 3.

A further preferred group of compounds of formula I are those of formula Ib



wherein

R₁ has the meaning given for formula I,

R₂^b is chlorine, bromine or methyl, and

R₄^b is C₃-7alkyl, C₃-7cycloalkyl or adamantyl.

Alkyl groups and moieties in the compounds of formulae I, Ia or Ib may be straight- or branched-chain.

For the above formula Ia, the following significances, as well as combinations, thereof are preferred:

1. R₁ is hydrogen or methyl, especially hydrogen.
2. R₂ is hydrogen.
3. R₃^a is C₃-5alkyl, especially n-propyl.
4. R₄^a is as previously defined under (ii): R₄^a is especially: phenyl; phenyl substituted by one or two members selected from the group consisting of methyl, methoxy, methylthio, hydroxy and nitro; phenyl substituted at two adjacent carbon atoms by the divalent residue of formula -O-CH₂-O-; or 2,3-dihydrobenzofuryl-5.

For the above formula Ib, the following significances, as well as combinations thereof, are preferred:

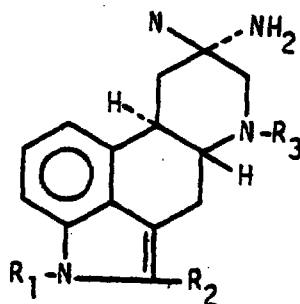
1. R₁ is hydrogen or methyl, especially hydrogen.
2. R₄^b is C₃-7alkyl, especially branched-chain C₃-7alkyl, in particular branched-chain C₃-5alkyl, most preferably t.butyl.

In one group of compounds of formula I, R_4 is C_3 -7alkyl; C_3 -7cycloalkyl; adamantyl; phenyl; phenyl substituted by one or two members selected from the group consisting of C_1 -3alkyl, C_1 -3alkoxy, C_1 -3alkylthio, hydroxy, amino and mono- and di- $(C_1$ -3alkyl)-amino; or phenyl substituted at two adjacent carbon atoms by a divalent residue of formula $-O-CH_2-O-$ or $-Z-(CH_2)_n-$, wherein Z is oxygen or sulphur and n is 2 or 3.

In one group of compounds of formula Ia, R_4^a is (i) C_3 -7alkyl or C_3 -7cycloalkyl; or (ii) phenyl; phenyl substituted by one or two members selected from the group consisting of C_1 -2alkyl, C_1 -2alkoxy, C_1 -2alkylthio and hydroxy; or phenyl substituted at two adjacent carbon atoms by a divalent residue of formula $-O-CH_2-O-$ or $-Z-(CH_2)_n-$ wherein Z is oxygen or sulphur and n is 2 or 3.

The present invention also provides a process for the production of the compounds of formula I and their acid addition salts, which process comprises:

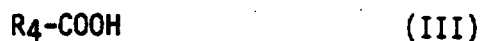
a) reacting a compound of formula II



(II)

13

wherein R_1 , R_2 and R_3 have the meanings given above with a compound of formula III



wherein R_4 has the meaning given above, or a reactive functional derivative thereof;

- b) Chlorinating or brominating a compound of formula I wherein R_2 is hydrogen to produce the corresponding compound of formula I wherein R_2 is chlorine or bromine; or
- c) N-(C₁-4alkylating) a compound of formula I wherein R_1 is hydrogen to produce a corresponding compound of formula I wherein R_1 is C₁-4alkyl;

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

Process step a) may be carried out in accordance with standard procedures. Suitable reactive functional derivatives of the compounds of formula III include e.g. the corresponding acyl halides, in particular chlorides, and imidazolides. Reaction with acylhalides is suitably effected in the presence of a base, such as triethylamine or Hünig-base. Reaction with imidazolides (obtained e.g. by reaction of the compound of formula III with N,N-carbonyldiimidazole) is suitably carried out in an inert solvent such as tetrahydrofuran or ethanol, e.g. at reflux temperature. Where a compound of formula I is employed as such, reaction may suitably be effected e.g. in the presence of propanephosphonic acid anhydride.

Process step b) may also be carried out in accordance with known techniques, using standard chlorinating or brominating agents such as N-Br- or N-Cl-succinimide, sulphuryl chloride or pyrrolidonehydrobromideperbromide. The reaction is conveniently performed in the presence of an inert diluent or solvent such as methylene chloride or tetrahydrofuran.

Process step c) may be carried out in accordance with known methods for the N-alkylation of indolines, e.g. employing a compound of formula IV



wherein R_1^1 is C_{1-4} alkyl and X is a leaving group, e.g. a halogen atom, in particular chlorine, fluorine or bromine atom, or methane- or p-toluene-sulfonyloxy group. The reaction is suitably carried out in the presence of an inert solvent or diluent such as dimethylsulfoxide, preferably in the presence of an acid binding agonist such as KOH.

The starting materials of formula II are known or may be produced analogously to the known compounds and in accordance with known procedures. The starting materials for steps b) and c) may be prepared in accordance with process step a).

The compounds of formula I may be recovered from the initially obtained reaction medium as such (i.e. in free base form) or in acid addition salt form e.g. in the form of their pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable acid addition salts include both such salts with inorganic acids, for example the hydrochloride salts, as well as such salts with organic acids, for example the oxalates and maleates.

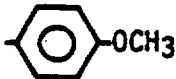
The following examples are illustrative of the processes for the production of the subject compounds:

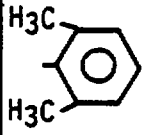
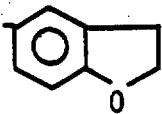
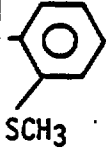
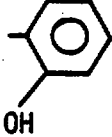
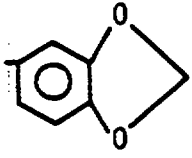
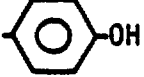
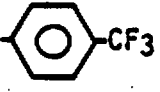
EXAMPLE 1:

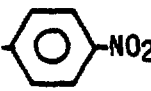
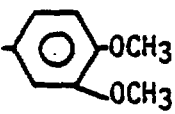
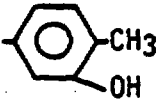
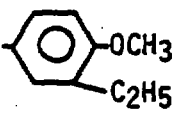
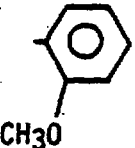
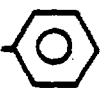
Preparation of 8 α -benzoylamino-6-n-propylergoline

1.4 ml benzoylchloride in 5 ml CH₂Cl₂ are added drop-wise with stirring at 5 - 10 ° C to a suspension of 3.0 g 8 α -amino-6-n-propylergoline in 100 ml CH₂Cl₂ and 2.0 ml triethylamine. The obtained reaction mixture is stirred for 15 to 20 hours at 20 ° C and then washed thoroughly 2 x with 25 ml 2N NaOH and H₂O. The organic phase is dried over MgSO₄, filtered and evaporated. The residue (pale brown foam) is dissolved in ethanol, and crystallised as the hydrobromide by addition of equivalent amounts of HBr in acetic acid. M.P. on recrystallisation from C₂H₅OH/H₂O (80 : 2) = 290 ° with decomposition.

The following compounds of formula I in which R₁ = hydrogen are obtained analogously:

EXAMPLE	R ₂	R ₃	R ₄	M.P. ° C (form)
2	H	-(CH ₂) ₂ -CH ₃	-C(CH ₃) ₃	328-330° (Hydro-chloride)
3	H	-(CH ₂) ₂ -CH ₃	Adamantyl-1	from 265 ° (Base)
4	H	-(CH ₂) ₂ -CH ₃	-C(CH ₃) ₂ -C ₂ H ₅	129 ° (Base)
5	H	-CH(CH ₃) ₂	-C(CH ₃) ₃	from 120 ° (Base)
6	H	-(CH ₂) ₂ -CH ₃		208-211° (Mesylate)

EXAMPLE	R ₂	R ₃	R ₄	M.P. ° C (form)
7	H	-(CH ₂) ₂ -CH ₃		Base. Compounds obtained as an amorphous powder - for characterisation see NMR data following.
8	H	-(CH ₂) ₂ -CH ₃		
9	H	-(CH ₂) ₂ -CH ₃		
10	H	-(CH ₂) ₂ -CH ₃		
11	H	-(CH ₂) ₂ -CH ₃		235-237° (Hydro-chloride)
12	H	-(CH ₂) ₂ -CH ₃		188-190° (Base)
13	H	-(CH ₂) ₂ -CH ₃		253-255° (½ Citrate)
14	H	-(CH ₂) ₂ -CH ₃		212-214° (½ Fumarate)

EXAMPLE	R ₂	R ₃	R ₄	M.P. ° C (form)
15	H	-(CH ₂) ₂ -CH ₃		230-233° (Hydrochloride)
16	H	-(CH ₂) ₂ -CH ₃		184-186° (Oxalate)
17	H	-(CH ₂) ₂ CH ₃		220-225° (Oxalate)
18	H	-(CH ₂) ₂ CH ₃		from 110° (Base)
19	CH ₃	CH ₃		Base. Amorphous powder. See NMR data following.
20	CH ₃	CH ₃		201-202° (Base)
21	CH ₃	CH ₃	-C(CH ₃) ₃	325-330° (Hydrochloride)
22	CH ₃	CH ₃	-CH(CH ₃) ₂	200-204° (Base)
23	CH ₃	CH ₃	-C(CH ₃) ₂ -C ₂ H ₅	210-212° (Base)
24	CH ₃	CH ₃	Adamantyl-1	from 250° (Base)

EXAMPLE	R ₂	R ₃	R ₄	M.P. ° C (form)
25	CH ₃	-(CH ₂) ₂ CH ₃		Base. Amorphous powder. See NMR data following.
26	CH ₃	-(CH ₂) ₂ CH ₃	-C(CH ₃) ₃	211-212° (Base)
27	H	CH ₃	Adamantyl-1	> 290° (Base)
28	H	CH ₃	-C(CH ₃) ₂ -C ₂ H ₅	153° (Base)
29	H	CH ₃		228-230° (Base)
30	H	CH ₃	-CH(CH ₃) ₂	170-171° (Base)

The starting material required for the preparation of the compounds of examples 19 to 24, namely 8 α -amino-2,6-dimethyl-ergoline, may be prepared as follows:

a) Preparation of 2-methyl-9,10-dihydrolysergic acid methyl ester

25 g 2-methyl-lysergic acid in 350 ml H₂O and 12.4 ml triethylamine are hydrogenated under normal pressure and at room temperature employing 5 % Pd/C. After up-take of the calculated amount of H₂, the reaction mixture is filtered

over Hyflo concentrated to half volume and adjusted to pH 6 by addition of 1N HCl. The obtained crystalline product is filtered off, dried, taken up in $\text{CH}_3\text{OH}/\text{HCl}$ and the obtained suspension stirred at room temperature for 2 - 3 days until full conversion as determined by thin-layer chromatography. The product is evaporated and subjected to distribution between sodium carbonate and ethyl acetate. After drying and evaporating the title compound is obtained as crystals, which are then rubbed with ethyl ether. M.P. = 180 - 182 ° C.

b) Preparation of 2-methyl-9,10-dihydroisolysergic acid methyl ester

43.4 ml of 1.65 molar butyllithium are added at - 50 ° C under argon to 200 ml tetrahydrofuran and 10.7 ml diisopropylamine. 9.5 g of the product of step a) in 100 ml tetrahydrofuran are added drop-wise after 30 mins. After allowing to stand for 1 hour at - 20 ° C the pH is adjusted to 7 by the addition of 10 % HCl. The mixture is warmed to room temperature, and the organic phase separated and washed 2 x with saturated brine. The title compound is obtained after drying and evaporation, filtration of the obtained oil using silica gel and $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98 : 2) as eluant and crystallisation from isopropanol. M.P. = 174 - 176 ° C.

c) Preparation of 2-methyl-9,10-dihydrolysergic acid hydrazide

5.95 g hydrazine hydrochloride and 6.8 ml hydrazine hydrate are added to 8.5 g of the product of step b) in 250 ml n-propanol and the obtained reaction mixture heated under reflux. The product is concentrated to half volume, filtered

and or washed with H₂O and filtered by suction to yield the title compound. M.P. = 250 ° C with decomposition.

d) Preparation of 8 α -amino-2,6-dimethyl-ergoline

1.38 g aqueous sodium nitrite are added drop-wise with ice-cooling and stirring to 7.8 g of the product of step c) in 220 ml 0.2 N HCl until the pH is ca. 2. When reaction is completed I/Cd paper shows a slight excess of HNO₂. The suspension is stirred for a further 30 mins. and added drop-wise to 100 ml 0.4 N, refluxing HCl. A clear solution is obtained which is cooled to room temperature, rendered alkaline with 2N soda solution and filtered. The obtained title compound is taken up in C₂H₅OH/ethylacetate (1 : 1), treated with active charcoal, filtered, concentrated and crystallised from methanol. M.P. = 240 ° C with decomposition.

The 8 α -amino-2-methyl-6-n-propyl-ergoline required as starting material for the production of the compounds of examples 25 and 26, may be obtained in conventional manner from the product of step d) above, via demethylation and n-propylation at the 6-position.

EXAMPLE 31:

Preparation of 2-bromo-6-n-propyl-8 α -pivaloylamino-ergoline

4.6 g pyrrolidonehydropromideperbromide in 100 ml tetrahydrofuran are added drop-wise to 3.1 g 6-n-propyl-8 α -pivaloylamino-ergoline (see example 2) in 100 ml tetrahydrofuran pre-cooled to 0 ° C. After reaction for 2 hours, 1N potassium carbonate is

added and the mixture extracted with methylene chloride. The organic phases are dried over Na_2SO_4 , concentrated and the residue chromatographed using 100 g silica gel and toluene/ethylacetate (2 : 1) as eluant. The title compound is obtained on crystallisation from ethylether/hexane. M.P. = 182 - 183 ° C.

EXAMPLE 32:

Preparation of 2-chloro-6-n-propyl-8 α -pivaloylamino-ergoline

1 g silica gel are added to 2 g 6-n-propyl-8 α -pivaloylamino-ergoline (example 2) in 50 ml methylene chloride, pre-cooled to 0 ° C. 0.503 ml sulfurylchloride are added drop-wise and the reaction mixture stirred for 4 hours. 1N potassium carbonate solution is added, the mixture extracted with methylene chloride, dried over Na_2SO_4 and concentrated. The residue is chromatographed on 50 g silica gel using toluene/ethylacetate (2 : 1) as eluant to yield the title compound. M.P. = 146 - 147 ° C.

The following compounds of formula I in which $\text{R}_1 = \text{H}$ may be prepared analogously to the above examples:

EXAMPLE	R_2	R_3	R_4	M.P. ° C (form)
33	Br	CH_3	$-\text{C}(\text{CH}_3)_3$	211-212° (Base)
34	Cl	CH_3	$-\text{C}(\text{CH}_3)_3$	215-216° (Base)
35	Cl	CH_3	$-\text{CH}_2-\text{C}(\text{CH}_3)_3$	192-193° (Base)
36	Cl	CH_3	$-(\text{CH}_2)_2-\text{CH}_3$	116-117° (Base)

23

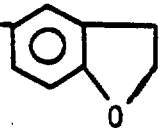
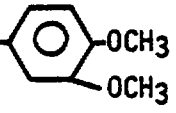
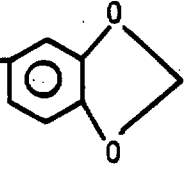
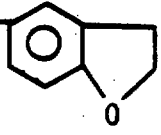
EXAMPLE	R ₂	R ₃	R ₄	M.P. ° C (form)
37	Cl	CH ₃	-CH(CH ₃) ₂	141-142° (Base)
38	Br	-(CH ₂) ₂ -CH ₃		235-237° (Hydro-bromide)
39	Cl	-(CH ₂) ₂ -CH ₃		213-214° (Base)

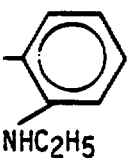
EXAMPLE 40:

Preparation of 1-methyl-6-n-propyl-8α-(2,3-dihydro-5-benzofuranylamino)-ergoline

696 mg finely powdered KOH and 0.77 ml methyl iodide are added to 4.1 g 6-n-propyl-8α-(2,3-dihydro-5-benzofuranylamino)-ergoline (example 9) in 25 ml dimethylsulfoxide. The reactive mixture is stirred for 5 hours, poured onto 150 ml H₂O, extracted with ethyl acetate, dried over Na₂SO₄ and concentrated. The residue is chromatographed on 100 g silica gel using methylene chloride/methanol (98 : 2) as eluant. M.P. = 137 - 138 ° C.

The following compounds of the formula I may be prepared analogously:

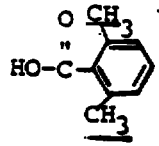
EXAMPLE	R ₁	R ₂	R ₃	R ₄	M.P. ° C (form)
41	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃		136-140° (½ Fumarate)
42	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃		142-143° (Base)
43	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃		Base. Amorphous powder. See NMR data following.
44	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃		158-159° (Base)
45	-C ₂ H ₅	H	-(CH ₂) ₂ CH ₃		112-115° (Base)
46	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃	-C(CH ₃) ₃	187-188° (Base)
47	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃	Adamantyl-1	214-215° (Base)
48	-CH(CH ₃) ₂	H	-(CH ₂) ₂ CH ₃	-C(CH ₃) ₂ -C ₂ H ₅	192° (Base)
49	-C ₂ H ₅	CH ₃	CH ₃	-C(CH ₃) ₃	149-150° (Base)
50	-CH(CH ₃) ₂	H	CH ₃	-C(CH ₃) ₃	162-163° (Base)

EXAMPLE	R ₁	R ₂	R ₃	R ₄	M.P. °C (form)
51	CH ₃	H	CH ₃	-C(CH ₃) ₃	Base. Amorphous powder - see NMR data following.
52	-CH(CH ₃) ₂	H	CH ₃		191 - 192 (Base)

NMR Data - Compounds of Examples 7, 8, 9, 10, 19, 25, 43 and 51:

The following selected, characteristic peaks were observed using NMR spectroscopy, with tetramethyl as reference at 0.0 ppm.

EXAMPLE 7:

NMR (CDCl₃, 90 MHz): 0,88 (t, 3H, J = 7Hz, CH₃-CH₂-); 2,35 (s, 6H, ); 4,65 (m, 1H, H-C₈); 6,7-7,3 (m, 9H, arom. H H-C₂, CONH); 8,0 (broad, 1H, N-H).

Example 8:

NMR (CDCl₃, 90 MHz): 0,91 (t, 3H, J = 7Hz, CH₃-CH₂-); 4,6 (t, 2H, J = 8, -O-CH₂-); 4,5 (m, 1H, H-C₈); 6,7-7,8 (m, 9H, arom. H, H-C₂, CONH); 8,1 (broad, 1H, N-H).

EXAMPLE 9:

NMR (CDCl₃, 360 MHz): 0,9 (t, 3H, J = 7Hz, CH₃-CH₂-);
2,45 (s, 3H, -S-CH₃); 4,58 (m, 1H, H-C₈);
6,9-7,6 (m, 9H, arom. H, H-C₂); 7,9 (1H, N-H).

EXAMPLE 10:

NMR (CDCl₃, 90 MHz): 0,98 (t, 3H, J = 7Hz, CH₃-CH₂);
2,5-3,6 (m, 9H, H-C₇, H-C₁₀, H-C₅-H-C_{4ax}, H-C_{9eq}, N-CH₂-);
4,55 (m, 1H, H-C₈); 6,7-7,6 (m, 9H, arom. H, CONH, H-C₂);
7,92 (broad, 1H, N-H).

EXAMPLE 19:

NMR (CDCl₃, 90 MHz): 2,4 (s, 3H, CH₃-C₂); 2,5 (s, 3H, N-CH₃);
3,92 (s, 3H, O-CH₃); 4,6 (m, 1H, H-C₈); 6,75-7,55 (m, 6H, arom. H)
7,75 (broad, 1H, N-H); 8,1-8,3 (m, 1H, arom. H); 8,8-9,0 (m, 1H, CONH).

EXAMPLE 25:

NMR (CDCl₃, 90 MHz): 0,98 (t, 3H, J = 7Hz, CH₃-CH₂);
2,4 (s, 3H, C₂-CH₃); 4,6 (m, 1H, H-C₈); 6,8-7,9 (m, 10H,
arom. H, N-H, CONH).

EXAMPLE 43:

NMR (CDCl₃, 360 MHz): 0,97 (t, 3H, J = 7Hz, CH₃-CH₂-);
1,5 (m, 8H, N- $\begin{matrix} \text{CH}_2 \\ \text{CH}_3 \end{matrix}$, CH₃-CH₂-); 3,91 (s, 3H, O-CH₃); 3,95 (s, 3H,
O-CH₃); 6,8-7,5 (m, 8H, arom. H, CONH).

20

EXAMPLE 51:

NMR (CDCl₃, 90 MHz): 1,2 (s, 9H, t-Butyl); 2,42 (s, 3H, N₆-CH₃);
3,76 (s, 3H, N₁-CH₃); 6,68-7,28 (m, 5H, arom.-H, CONH).

The compounds of formula I and their pharmaceutically acceptable acid addition salts possess pharmacological activity as can be shown in standard animal test methods, and are accordingly indicated for use as pharmaceuticals.

In particular the said compounds and salts possess prolactin (PRL) secretion inhibiting activity as demonstrated e.g. by inhibition of basal prolactin secretion in male rats in the method described by Flückiger et al, *Experientia* 34, 1330 (1970). Compounds of formula I exhibit activity in this test method at dosages of from 0.0005 to 0.5 mg/kg s.c..

In addition compounds of formula I, in particular compounds of formula Ia, and their pharmaceutically acceptable acid addition salts possess leutenising hormone (LH) secretion inhibiting activity as demonstrated by ovulation inhibition in the following test method [c.f. Marko et al., *Life Sciences* 33, 233 - 240 (1983)]:

Female rats (200 - 250 g) of regular 4 day cycle receive test substance during pro-oestrus at ca. 13.00 and 16.00 hrs. The next morning they are sacrificed, the oviducts examined microscopically and the ova counted. Ovulation is deemed to be inhibited only if no ova are found. The average number of ova counted for each of a series of test animal groups receiving test substance at differing dosages is also recorded in order to permit determination of ED₅₀ values i.e. dosages at which 50 % ovulation inhibition is achieved. Compounds of formula Ia exhibit activity in this test method at dosages of from 0.05 to 10.0 mg/kg i.v..

Furthermore compounds of formula I, in particular compounds of formula Ib, and their pharmaceutically acceptable acid addition salts, possess apomorphine antagonistic activity as demonstrated

29

in the test method described by Jansson et al., *Arz. Forsch.* 10, 1003, (1960). Thus compounds of formula Ib inhibit apomorphine (10 mg/kg s.c.) induced, stereotyped gnawing over periods of several hours, at dosages of from 0.032 mg/kg s.c..

As will be appreciated, activity as PRL secretion inhibitors as demonstrable in the relevant test method described above is also demonstrative of dopamine antagonist activity. Furthermore apomorphine antagonist activity as demonstrable (in particular in respect of compounds of formula Ib) in the relevant test method described above is also demonstrable of dopamine agonist activity. Thus compounds of e.g. formula Ib may be characterised as having a dual dopamine agonist/antagonist activity profile.

In view of their PRL secretion inhibiting activity, compounds of formula I and their pharmaceutically acceptable acid addition salts are indicated for use as PRL secretion inhibitors, e.g. in the treatment of conditions or disorders for which reduction of prolactin levels is indicated, for example for the treatment of galactorrhoea including post-partum galactorrhoea, for the treatment of prolactin-dependent menstrual disorders including amenorrhoea, for the inhibition of lactation including post-partum lactation and morbid lactation as well as for the treatment of hyperprolactinaemic hypogonadism in males and females and of prolactinoma. Furthermore in view of concomitant dopamine agonist activity compounds of formula I and their pharmaceutically acceptable acid addition salts are also indicated for use as dopamine agonists, e.g. for the treatment of Morbus Parkinson.

In view of their LH secretion inhibiting activity compounds of formula I, in particular compounds of formula Ia, and their pharmaceutically acceptable acid addition salts are further



indicated for use in the treatment of disorders having an aetiology associated with or modulated by LH secretion or having an aetiology in which the physiological regulation of LH secretion is implicated, for example in the treatment of prostate hypertrophy, in the treatment of menopausal syndrome, in particular post-menopausal hot flashes, as well as the treatment of mammary- and prostate-carcinoma.

In view of their apomorphine antagonistic activity compounds of formula I, in particular compounds of formula Ib, and their pharmaceutically acceptable acid addition salts are indicated for use as neuroleptic agents, for example for the treatment of schizophrenia.

It will be further be appreciated that where PRL inhibiting activity is accompanied by apomorphine antagonistic activity, e.g. as in the case of compounds of formula Ib, and the compounds exhibit a dopamine antagonist profile component, the subject compounds and their pharmaceutically acceptable acid addition salts will be of particular interest in relation to their indicated utility as PRL secretion inhibitors, having regard to the reduced likelihood of undesirable side-effects (e.g. emetic activity) occurring at endocrinologically active dosages.

For the above uses, the dosage required will of course vary depending on e.g. the particular compound employed, the mode of administration, the particular condition to be treated and the effect desired.

However an indicated daily dosage is in the range of:

31

-24-

- 1) from about 0.05 to about 5.0 mg for use in PRL secretion inhibition;
- 2) from about 1 to about 10 mg for use in LH secretion inhibition; and
- 3) from about 1 to about 40 mg, for neuroleptic use,

of compound of formula I, conveniently administered in divided doses of 2 to 4x/day in unit dosage form or in sustained release form. Suitable unit dosage forms accordingly comprise:

- 1) from about 0.01 to about 2.5 mg;
- 2) from about 0.25 to about 5.0 mg; and
- 3) from about 0.25 to about 20.0 mg,

(according to intended utility) of compound of formula I together with one or more pharmaceutically acceptable diluents or carriers therefore.

The compounds of formula I may be administered as such or in the form of their pharmaceutically acceptable acid addition salts. Such salts exhibit the same order of activity as the free bases.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of tablets or capsules, or parenterally e.g. in the form of injectible solutions or suspensions.

In accordance with the foregoing the present invention also provides.

- 1) A pharmaceutical composition comprising a compound of formula I as hereinbefore defined or a pharmaceutically acceptable

acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor;

- 2) A compound of formula I as hereinbefore defined or pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical, i.e. for use in therapy, for example: for use as an PRL secretion inhibitor or for use as a dopamine agonist; or (in particular in the case of compounds of formula Ia as hereinbefore defined and their pharmaceutically acceptable acid addition salts) for use as an LH secretion inhibitor; or (in particular in the case of compounds of formula Ib as hereinbefore defined and their pharmaceutically acceptable acid addition salts) for use as a neuroleptic; and especially for use in any of the specific indications hereinbefore recited in relation to such use; as well as

- 3) A compound for use in

- 3.1.a inhibiting PRL secretion
- 3.1.b treating Morbus Parkinson
- 3.2 inhibiting LH secretion; or
- 3.3 effecting neuroleptic treatment,

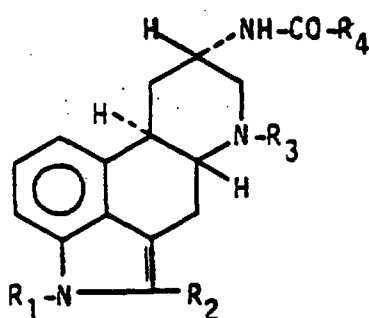
e.g. for treating any of specific conditions hereinbefore recited in relation to such treatment, in a subject in need of such treatment.

33

26

CLAIMS:

1. A compound of formula I



(I)

wherein

R₁ is hydrogen or C₁₋₄alkyl,

R₂ is hydrogen, chlorine, bromine or methyl,

R₃ is C₁₋₅alkyl or C₃₋₅alkenyl in which the double bond is not at the carbon atom adjacent to the nitrogen atom, and

R₄ is C₃₋₇alkyl; C₃₋₇cycloalkyl; adamantyl; phenyl; phenyl substituted by one or more members selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, trifluoromethyl, hydroxy, nitro, amino and mono- and di-(C₁₋₃alkyl)-amino; or phenyl bearing a condensed non-aromatic, heterocyclic ring having 5- or 6-ring members including 1 or 2 hetero atoms selected from the group consisting of oxygen and sulphur,

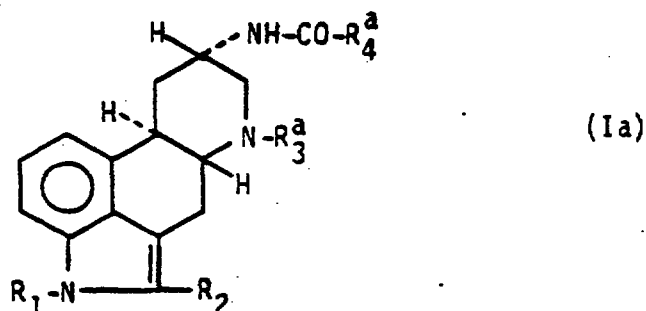
with the proviso that when R₁ and R₂ are both hydrogen and R₃ is methyl, R₄ is other than t.butyl, or acid addition salt thereof.



34

27

2. A compound according to claim 1 of formula Ia



wherein

R_1 and R_2 have the meanings given in claim 1,

R_3^a is C₂-5alkyl or C₃-5alkenyl in which the double bond is not at the carbon atom adjacent to the nitrogen atom, and

R_4^a is C₃-7alkyl; C₃-7cycloalkyl; phenyl; phenyl substituted by one or two members selected from the group consisting of C₁-2alkyl, C₁-2alkoxy, C₁-2alkylthio, hydroxy and nitro; or phenyl substituted at two adjacent carbon atoms by a divalent residue of formula -O-CH₂-O- or -Z-(CH₂)_n-, wherein Z is oxygen or sulphur and n is 2 or 3,

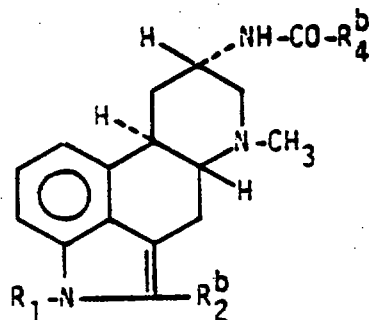
or acid addition salt thereof.

3. A compound according to claim 1 of formula Ib



35

28



(Ib)

wherein

R_1 has the meanings given in claim 1.

R_2^b is chlorine, bromine or methyl, and

R_4^b is C₃-7alkyl, C₃-7cycloalkyl or adamantyl, or acid addition salt thereof.

4. A compound of formula I as defined in claim 1, wherein R_4 is C₃-7alkyl; C₃-7cycloalkyl; adamantyl; phenyl; phenyl substituted by one or two members selected from the group consisting of C₁-3alkyl, C₁-3alkoxy, C₁-3alkylthio, hydroxy, amino and mono- and di-(C₁-3alkyl)-amino; or phenyl substituted at two adjacent carbon atoms by a divalent residue of formula -O-CH₂-O- or -Z-(CH₂)_n-, wherein Z is oxygen or sulphur and n is 2 or 3, or acid addition salt thereof.
5. A compound of formula Ia as defined in claim 2, wherein R_4^a is C₃-7alkyl; C₃-7cycloalkyl; phenyl; phenyl substituted by one or two members selected from the group consisting of C₁-2alkyl, C₁-2alkoxy, C₁-2alkylthio and hydroxy; or phenyl substituted at two adjacent carbon atoms by divalent residue of formula -O-CH₂-O- or -Z-(CH₂)_n- wherein Z is oxygen or sulphur and n is 2 or 3, or acid addition salt thereof.



6. The compound of formula I as illustrated in claim 1 in which R_1 is hydrogen, R_2 and R_3 are each methyl, and R_4 is t.-butyl, or acid addition salt thereof.

7. The compound of formula I as illustrated in claim 1, wherein R_1 is hydrogen, R_2 is chlorine, R_3 is methyl and R_4 is t.-butyl or acid addition salt thereof.

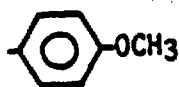
8. ~~Preparation of~~ 8 α -benzoylamino-6-n-propylergoline.

9. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is $-C(CH_3)_3$.

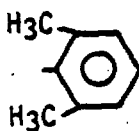
10. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is Adamantyl-1.

11. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is $-C(CH_3)_2-C_2H_5$.

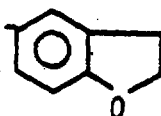
12. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-C(CH_2)_2-CH_3$, R_4 is



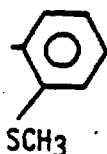
13. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



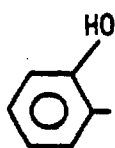
14. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



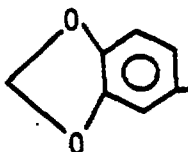
15. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



16. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



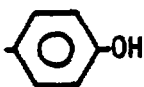
17. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



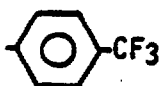
18. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



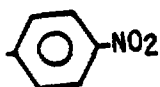
19. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



20. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



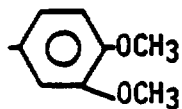
21. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



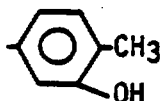
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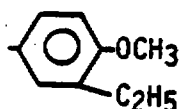
22. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2-CH_3$, R_4 is



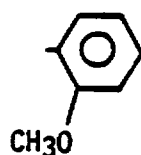
23. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



24. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



25. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is CH_3 , R_4 is



26. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is CH_3 , R_4 is



27. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is $-CH(CH_3)_2$, R_4 is $-C(CH_3)_3$.

28. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is CH_3 , R_4 is $-CH(CH_3)_2$.

29. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is CH_3 , R_4 is $-C(CH_3)_2-C_2H_5$.

30. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is CH_3 , R_4 is Adamantyl-1.



* C L M S *

31. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is $-(\text{CH}_2)_2\text{CH}_3$, R_4 is



32. A compound of claim 1 wherein R_1 is hydrogen, R_2 is CH_3 , R_3 is $-(\text{CH}_2)_2\text{CH}_3$, R_4 is $-\text{C}(\text{CH}_3)_3$.

33. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is CH_3 , R_4 is Adamantyl-1.

34. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is CH_3 , R_4 is $-\text{C}(\text{CH}_3)_2-\text{C}_2\text{H}_5$.

35. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is CH_3 , R_4 is



36. A compound of claim 1 wherein R_1 is hydrogen, R_2 is H, R_3 is CH_3 , R_4 is $-\text{CH}(\text{CH}_3)_2$.

37. 2-bromo-6-n-propyl-8 α -pivaloylamino-ergoline.

38. 2-chloro-6-n-propyl-8 α -pivaloylamino-ergoline.

39. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Br, R_3 is CH_3 , R_4 is $-\text{C}(\text{CH}_3)_3$.

40. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Cl, R_3 is $-\text{CH}(\text{CH}_3)_2$, R_4 is $-\text{C}(\text{CH}_3)_3$.

41. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Cl, R_3 is CH_3 , R_4 is $-(\text{CH}_2)_2-\text{CH}_3$.

42. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Cl, R_3 is CH_3 , R_4 is $-\text{CH}(\text{CH}_3)_2$.

43. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Br, R_3 is $-(\text{CH}_2)_2-\text{CH}_3$, R_4 is



44. A compound of claim 1 wherein R_1 is hydrogen, R_2 is Cl, R_3 is $-(CH_2)_2-CH_3$, R_4 is

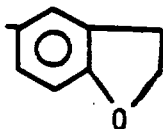


45. 1-methyl-6-n-propyl-8 α -(2,3-dihydro-5-benzo-furanyl-amino)-ergoline.

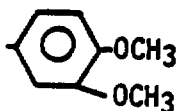
46. A compound of claim 1 wherein R_1 is $-(CH(CH_3)_2)$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



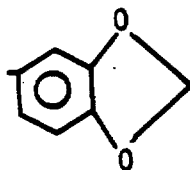
47. A compound of claim 1 wherein R_1 is $-(CH(CH_3)_2)$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



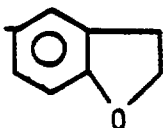
48. A compound of claim 1 wherein R_1 is $-(CH(CH_3)_2)$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



49. A compound of claim 1 wherein R_1 is $-(CH(CH_3)_2)$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



50. A compound of claim 1 wherein R_1 is $-C_2H_5$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is



51. A compound of claim 1 wherein R_1 is $-(CH(CH_3)_2)$, R_2 is H, R_3 is $-(CH_2)_2CH_3$, R_4 is $-C(CH_3)_3$.



52. A compound of claim 1 wherein R_1 is $-\text{CH}(\text{CH}_3)_2$, R_2 is H, R_3 is $-(\text{CH}_2)_2\text{CH}_3$, R_4 is Adamantyl-1.

53. A compound of claim 1 wherein R_1 is $-\text{CH}(\text{CH}_3)_2$, R_2 is H, R_3 is $-(\text{CH}_2)_2\text{CH}_3$, R_4 is $-(\text{CH}_3)_2-\text{C}_2\text{H}_5$.

54. A compound of claim 1 wherein R_1 is $-\text{C}_2\text{H}_5$, R_2 is CH_3 , R_3 is CH_3 , R_4 is $-\text{C}(\text{CH}_3)_3$.

55. A compound of claim 1 wherein R_1 is $-\text{CH}(\text{CH}_3)_2$, R_2 is H, R_3 is CH_3 , R_4 is $-\text{C}(\text{CH}_3)_3$.

56. A compound of claim 1 wherein R_1 is CH_3 , R_2 is H, R_3 is CH_3 , R_4 is $-\text{C}(\text{CH}_3)_3$.

57. A compound of claim 1 wherein R_1 is $-\text{CH}(\text{CH}_3)_2$, R_2 is H, R_3 is CH_3 , R_4 is

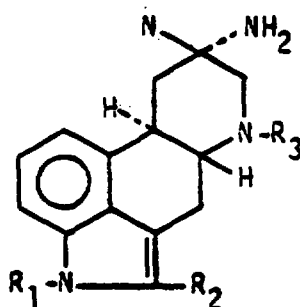


58. A compound of any one of claims 1 to 57 in free base form.

59. A compound of any one of claims 1 to 57 in acid addition salt form.

60. Process for the production of a compound of formula I as defined in claim 1 or acid addition salt thereof, which process comprises:

a) reacting a compound of formula II



(II)



wherein R_1 , R_2 and R_3 have the meanings given in claim 1, with a compound of formula III



wherein R_4 has the meaning given in claim 1;

- b) chlorinating or brominating a compound of formula I as defined in claim 1 wherein R_2 is hydrogen or produce the corresponding compound of formula I wherein R_2 is chlorine or bromine; or
 - c) $N(C_{1-4}alkylating)$ a compound of formula I as defined in claim 1 wherein R_1 is hydrogen to produce a corresponding compound of formula I wherein R_1 is $C_{1-4}alkyl$;
- and recovering the obtained compound of formula I as such or as an acid addition salt thereof.

61. A pharmaceutical composition comprising a compound as defined in any one of the claims 1 to 59 or pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

62. A compound as defined in any one of claims 1 to 59 or pharmaceutically acceptable acid addition salt thereof, for use as a pharmaceutical.

63. A compound as defined in any one of claims 1 to 59 or pharmaceutically acceptable acid addition salt thereof, for neuroleptic use.

