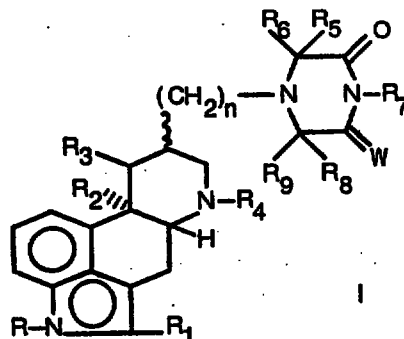


Description

The invention relates to ergoline derivatives and to a process for their preparation.

In DE-A-1 901 750 ergoline derivatives are described containing at the 8-position a piperazin ring connected by a methylen group. The ergoline derivatives have anti-depressant or anti-psychotic properties. From EP-A-0 126 968 ergoline derivatives are known in which the 8-substituent can be an oxo-substituted imidazole. Said compounds have anti-prolactinic and anti-hypertensive activity.

The invention provides ergoline derivatives having the general formula I



wherein R represents a hydrogen atom or a methyl group; R₁ represents a hydrogen or a fluorine, chlorine or bromine atom, a methyl or phenylthio group or an alkylthio group having from 1 to 4 carbon atoms; either R₂ represents a hydrogen atom or a methoxy group and R₃ represents a hydrogen atom or R₂ and R₃ together represent a chemical bond; R₄ represents a hydrocarbon group having from 1 to 4 carbon atoms; either each of R₅, R₆, R₇ and R₈ independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms or R₅ and R₆ are as above defined and R₅ and R₆ together represent an ethylene or trimethylene group; R₇ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a group of the general formula NR'R'' wherein either each of R' and R'' independently represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a C₁ to C₅ alkanoyl or benzoyl group or R' and R'' together with the nitrogen atom to which they are attached represent a heterocyclic ring; W represents an oxygen atom or two hydrogen atoms; and n is 0, 1 or 2; and further provides pharmaceutically acceptable salts of such ergoline derivatives.

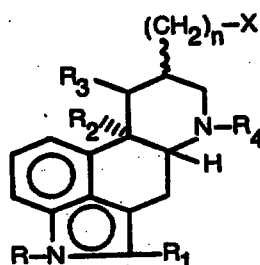
In the definition of R₄, a hydrocarbon group having from 1 to 4 carbon atoms is intended to include alkyl, cycloalkyl and unsaturated (both ethylenically and acetylenically) groups.

Representative moieties include methyl, ethyl, n-propyl, isopropyl, butyl, t-butyl, isobutyl, methylcyclopropyl, allyl and propargyl.

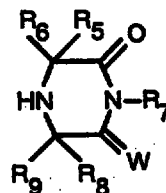
An alkyl group having from 1 to 4 carbon atoms is preferably methyl, ethyl, n-propyl, isopropyl or n-butyl group, most preferably a methyl group.

When R' and R'' together with the nitrogen atom to which they are bonded form a heterocyclic ring, this ring is preferably selected from the group consisting of pyrrolidine, piperidine, morpholine, pyrazole, imidazole and pyrrole.

The invention further provides a process for the preparation of the ergoline derivatives of the general formula I as above defined, the process comprising condensing an ergoline derivative of the general formula II with a piperazine derivative of the general formula III



II



III

wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, W and n are as above defined and X represents a chlorine or bromine atom or a mesyloxy or tosyloxy group. The condensation process is carried out in an organic solvent such as toluene, xylene, acetonitrile, dimethylformamide or dimethylsulphoxide in the presence of a catalytic amount of potassium or sodium iodide as a catalyst at temperature of from 80°C to 150°C for a

period of from 2 to 24 hours. The reaction may be carried out with an excess of the piperazine derivative which acts as an acid scavenger or with equimolar amounts of the reactant using an acid scavenger such as an inorganic carbonate or triethylamine. When the reaction is complete the solvent is evaporated off and the residue is purified by crystallization or chromatography according to well known techniques. The compounds of the general formula II and III are well known in the art or can be made from precursor compounds by well known reactions.

The ergoline derivatives according to the invention and their pharmaceutically acceptable salts exhibit from moderate to good anti-hypertensive activity and are useful anxiolytic and antipsychotic agents.

The profiles of the central sedative pharmacological activity were obtained by Irwin's observational assessment of mouse behaviour (Irwin, S. — *Psychopharmacologia, Berl.*, 13, 222, 1968), which also gives an indication of the orientative acute toxicity after 7 days observation, and by antagonism to the central apomorphine-induced stereotypes (climbing) in mice.

The results obtained with some compounds of the invention are reported in the Table

TABLE

Compound of Example No.	Apomorphine antagonism (ED ₅₀ , mg/kg p.o.)	Orientative acute toxicity (LD ₅₀ , mg/kg p.o.)
1	4.4	600
2	0.9	300
3	2.2	300
5	0.5	200

For the antagonism to central apomorphine-induced climbing (Protais, P. et al. — *Psychopharmacology*, 50, 1, 1976) the compounds were orally administered to male mice, in a dose range between 0.25 and 10 mg/kg, 60 minutes before the subcutaneous injection of 1 mg/kg of apomorphine. Hcl. The antagonism to apomorphine-induced climbing behaviour was evaluated 10 minutes after apomorphine administration.

The compounds of the invention also proved inactive in the induction of muscle relaxation (Irwin's test in the mouse) and motor incoordination (Rotarod test in the rat as described by Dunham, N. W. et al. — *J. Am. Pharm. Ass.* 46: 208, 1957) up to the oral dose of 10 mg/kg.

Accordingly, the invention further provides a pharmaceutical composition comprising an ergoline derivative having the general formula I or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

Compounds of formula I and their salts described herein may be administered by parenteral or oral route, preferably by oral route.

Depending on administration route, the compositions may be in the form of solid, semi-solid or liquid dosage form, such as, for example, tablets, pills, capsules, powders, liquids, suspensions or the like.

The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of formula I or the pharmaceutically acceptable salt thereof and, in addition, may include other medical agents, pharmaceutical agents, carriers, adjuvants, etc.

The dosage of the present drugs varies in accordance with the sex, age, condition or medical record of the patient, as well as according to the route or purpose of the administration. In general, the drugs may be administered as single doses or as divided doses so as to provide, say, about 0.001—5 mg/kg body weight per day of effective ingredient, preferably about 0.005—1 mg/kg body weight.

The pharmaceutical compositions containing the compounds of the invention are prepared according to conventional methods with the usual ingredients.

Thus, for oral administration, the pharmaceutical compositions containing the compounds of the invention are preferably tablets, pills or capsules which contain the active substance together with diluents, such as, for example, lactose, dextrose, sucrose, mannitol, sorbitol, sucrose, cellulose; lubricants, for instance, silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; or they may also contain binders, such as, for example, starches, gelatine, methyl-cellulose, gum-arabic, tragacanth,

polyvinylpyrrolidone; disintegrating agents, such as, for instance, starches, alginic acid, alginates; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations.

Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

Also the other pharmaceutical formulations containing the compounds of the invention may be prepared by known methods and they can be, for example, syrup or drops for the oral administration, sterile solutions for injection, or suppositories.

The following Examples illustrate the invention.

Example 1

6-Methyl-8 β -(3,5-dioxo-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_4 = CH_3$, $W = O$, $n = 1$)

A solution of 4.12 g of 6-methyl-8 β -tosyloxymethyl-ergoline, 2.2 g of piperazine-3,5-dione and 0.2 g of potassium iodide in 870 ml of dimethylformamide was heated at 80°C for 5 hours. The dimethylformamide was evaporated off; the residue, dissolved in methylene dichloride, was washed with water and saline and dried on anhydrous sodium sulphate. After filtration and removal of the solvent, the product was crystallized from methanol to give 2.8 g of the title compound, m.p. 260—262°C.

Example 2

1,6-Dimethyl-8 β -(3,5-dioxo-piperazin-1-ylmethyl)-ergoline

(I: $R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R = R_4 = CH_3$, $W = O$, $n = 1$)

Operating as in Example 1, but employing 1,6-dimethyl-8 β -tosyloxymethyl-ergoline in place of 6-methyl-8 β -tosyloxymethyl-ergoline, the title compound, m.p. 268—270°C, was obtained in 80% yield.

Example 3

6-Methyl-8 β -(3,5-dioxo-4-methyl-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_4 = R_7 = CH_3$, $W = O$, $n = 1$)

Operating as in Example 1, but employing 4-methyl-piperazine-3,5-dione in place of piperazine-3,5-dione, the title compound, m.p. 235—237°C, was obtained in 75% yield.

Example 4

6-Methyl-8 β -(3,5-dioxo-4-amino-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_4 = CH_3$, $R_7 = NH_2$, $W = O$, $n = 1$)

Operating as in Example 1, but employing 4-aminopiperazine-3,5-dione in place of piperazine-3,5-dione, the title compound, m.p. 210—212°C, was obtained in 65% yield.

Example 5

6-Methyl-9,10-didehydro-8 β -(3,5-dioxo-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_2 + R_3 = \text{chemical bond}$, $R_4 = CH_3$, $W = O$, $n = 1$)

Operating as in Example 1, but employing 9,10-didehydro-6-methyl-8 β -tosyloxymethyl-ergoline in place of 6-methyl-8 β -tosyloxymethyl-ergoline, the title compound, m.p. 208—210°C, was obtained in 68% yield.

Example 6

6-Methyl-8 β -(3-oxo-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_4 = CH_3$, $W = H_2$, $n = 1$)

Operating as in Example 1, but employing piperazine-2-one in place of piperazine-3,5-dione, the title compound, m.p. 238—240°C, was obtained in 75% yield.

Example 7

6-Methyl-9,10-didehydro-8 β -(3,5-dioxo-4-amino-piperazin-1-ylmethyl)-ergoline

(I: $R = R_1 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_2 + R_3 = \text{chemical bond}$, $R_4 = CH_3$, $R_7 = NH_2$, $W = O$, $n = 1$)

Operating as in Example 5, but employing 4-amino-piperazine-3,5-dione in place of piperazine 3,5-dione, the title compound, m.p. 224—226°C, was obtained in 62% yield.

Example 8

6-Methyl-8 β -(3,5-dioxo-4-phenyl-piperazino-1-ylmethyl)-ergoline

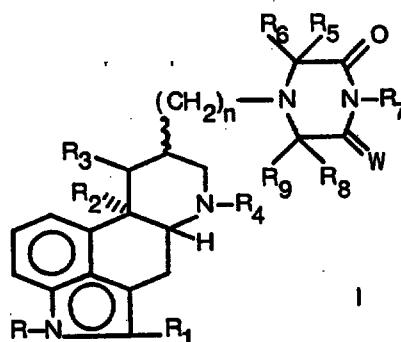
(I: $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_4 = CH_3$, $R_7 = \text{phenyl}$, $W = O$, $n = 1$)

Operating as described in Example 1, but employing 4-phenylpiperazine, 3,5-dione in place of piperazine 3,5-dione, the title compound, m.p. 260—262°C, was obtained in 70% yield.



Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An ergoline derivative having the general formula I



wherein R represents a hydrogen atom or a methyl group; R₁ represents a hydrogen or a fluorine, chlorine or bromine atom, a methyl or phenylthio group or an alkylthio group having from 1 to 4 carbon atoms; either R₂ represents a hydrogen atom or a methoxy group and R₃ represents a hydrogen atom or R₂ and R₃ together represent a chemical bond; R₄ represents a hydrocarbon group having from 1 to 4 carbon atoms; either each of R₅, R₆, R₈ and R₉ independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms or R₅ and R₆ are as above defined and R₈ and R₉ together represent an ethylene or trimethylene group; R₇ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a group of the general formula NR'R'' wherein either each of R' and R'' independently represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a C₁ to C₅ alkanoyl or benzoyl group or R' and R'' together with the nitrogen atom to which they are attached represent a heterocyclic ring; W represents an oxygen atom or two hydrogen atoms; and n is 0, 1 or 2; or a pharmaceutically acceptable salt of such ergoline derivative.

2. 6-Methyl-8β-(3,5-dioxo-piperazin-1-ylmethyl)-ergoline.

3. 1,6-Dimethyl-8β-(3,5-dioxo-piperazin-1-ylmethyl)-ergoline.

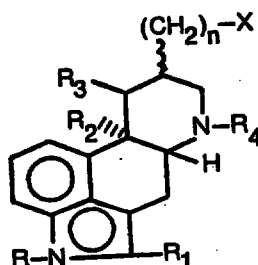
4. 6-Methyl-8β-(3,5-dioxo-4-methyl-piperazin-1-ylmethyl)-ergoline.

5. 6-Methyl-8β-(3,5-dioxo-4-amino-piperazin-1-ylmethyl)-ergoline.

6. 6-Methyl-9,10-didehydro-8β-(3,5-dioxo-piperazin-1-ylmethyl)-ergoline.

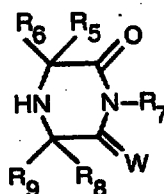
7. 6-Methyl-8β-(3-oxo-piperazin-1-ylmethyl)-ergoline.

8. A process for the preparation of an ergoline derivative according to claim 1, the process comprising condensing, in an organic solvent in the presence of potassium iodide or sodium iodide at from 80°C to 150°C for from 2 to 24 hours, an ergoline derivative of the general formula II



II

wherein R, R₁, R₂, R₃, R₄ and n are as defined in claim 1 and X represents a chlorine or bromine atom or a mesyloxy or tosyloxy group with a piperazine derivative of the general formula III



III

wherein R₅, R₆, R₇, R₈, R₉ and W are as defined in claim 1.

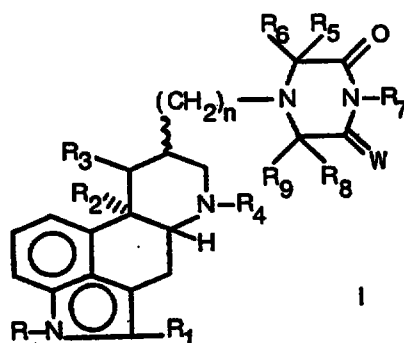
9. A process according to claim 8 in which the organic solvent is toluene, xylene, acetonitrile, dimethylformamide or dimethylsulphoxide.

10. A pharmaceutical composition comprising an ergoline derivative according to any of claims 1 to 7, an ergoline derivative prepared according to any of claims 8 to 9 or a pharmaceutically acceptable salt of such an ergoline derivative in admixture with a pharmaceutically acceptable diluent or carrier.

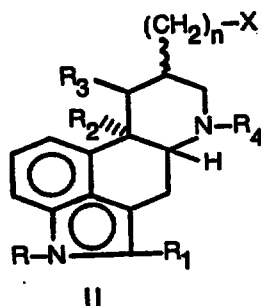
11. Use of an ergoline derivative according to any of claims 1 to 7, or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition having anti-hypertensive, anxiolytic or antipsychotic activities.

10 Claims for the Contracting State: AT

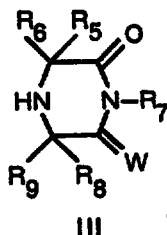
1. A process for the preparation of an ergoline derivative having the general formula I



wherein R represents a hydrogen atom or a methyl group; R₁ represents a hydrogen or a fluorine, chlorine or bromine atom, a methyl or phenylthio group or an alkylthio group having from 1 to 4 carbon atoms; either R₂ represents a hydrogen atom or a methoxy group and R₃ represents a hydrogen atom or R₂ and R₃ together represent a chemical bond; R₄ represents a hydrocarbon group having from 1 to 4 carbon atoms; either each of R₅, R₆, R₈ and R₉ independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms or R₅ and R₆ are as above defined and R₈ and R₉ together represent an ethylene or trimethylene group; R₇ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a group of the general formula NR'R'' wherein either each of R' and R'' independently represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a C₁ to C₅ alkanoyl or benzoyl group or R' and R'' together with the nitrogen atom to which they are attached represent a heterocyclic ring; W represents an oxygen atom or two hydrogen atoms; and n is 0, 1 or 2; or a pharmaceutically acceptable salt of such ergoline derivative, characterized in that in an organic solvent in the presence of potassium iodide or sodium iodide at from 80°C to 150°C for from 2 to 24 hours, an ergoline derivative of the general formula II



wherein R, R₁, R₂, R₃, R₄ and n are as defined in claim 1 and X represents a chlorine or bromine atom or a mesyloxy or tosyloxy group with a piperazine derivative of the general formula III



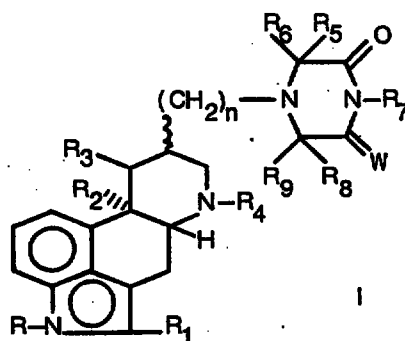
wherein R_5 , R_6 , R_7 , R_8 , R_9 and W have the above definition.

2. A process according to claim 1, characterized in that the organic solvent is toluene, xylene, acetonitrile, dimethylformamide or dimethylsulphoxide.

3. Use of a pharmaceutical composition comprising an ergoline derivative according to claim 1 or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition having anti-hypertensive, anxiolytic or antipsychotic activities.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

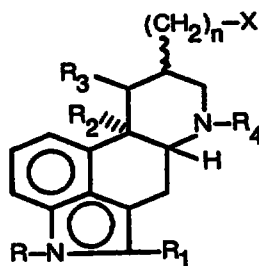
1. Ergolinderivat der allgemeinen Formel (I)



wobei R ein Wasserstoffatom oder eine Methylgruppe darstellt; R₁ ein Wasserstoffatom oder ein Fluoratom, Chloratom oder Bromatom, eine Methylgruppe oder eine Phenylthiogruppe oder eine Alkylthiogruppe mit 1 bis 4 Kohlenstoffatomen ist; entweder R₂ ein Wasserstoffatom oder eine Methoxygruppe und R₃ ein Wasserstoffatom darstellen, oder R₂ und R₃ zusammen eine chemische Bindung bilden; R₄ eine Kohlenwasserstoffgruppe mit 1 bis 4 Kohlenstoffatomen darstellt; entweder jeder der Substituenten R₅, R₆, R₈ und R₉ unabhängig voneinander ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen, oder R₅ und R₆ wie oben definiert sind und R₈ und R₉ zusammen eine Ethylen- oder Trimethylengruppe bilden; R₇ ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Phenylgruppe oder eine Gruppe der allgemeinen formel NR'R'' darstellen, wobei entweder jeder der Substituenten R' und R'' unabhängig voneinander ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder eine C₁₋₅-Alkanoyl- oder Benzoylgruppe darstellen, oder R' und R'' zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterozyklischen Ring bilden, darstellt; W ein Sauerstoffatom oder zwei Wasserstoffatome darstellt; und n 0, 1 oder 2 ist; oder ein pharmazeutisch verträgliches Salz solch eines Ergolinderivates.

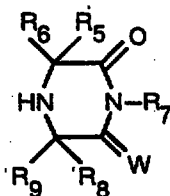
2. 6-Methyl-8β-(3,5-dioxo-piperazin-1-ylmethyl)-ergolin.
3. 1,6-Dimethyl-8β-(3,5-dioxo-piperain-1-ylmethyl)-ergolin.
4. 6-Methyl-8β-(3,5-dioxo-4-methyl-piperain-1-ylmethyl)-ergolin.
5. 6-Methyl-8β-(3,5-dioxo-4-amino-piperazin-1-ylmethyl)-ergolin.
6. 6-Methyl-9,10-didehydro-8β-(3,5-dioxo-piperazin-1-ylmethyl)-ergolin.
7. 6-Methyl-8β-(3-oxo-piperazin-1-ylmethyl)-ergolin.

8. Verfahren zur Herstellung eines Ergolinderivates nach Anspruch 1, wobei das Verfahren die Kondensation eines Ergolinderivates der allgemeinen Formel (II)



wobei R, R₁, R₂, R₃, R₄ und n wie im Anspruch 1 definiert sind und X ein Chlor- oder Bromatom oder eine Mesyloxy- oder Tosyloxygruppe darstellt, mit einem Piperazinderivat der allgemeinen Formel (III)





III

wobei R_5 , R_6 , R_7 , R_8 , R_9 und W wie in Anspruch 1 definiert sind, in einem organischen Lösungsmittel in Gegenwart von Kaliumjodid oder Natriumjodid bei 80° bis 150°C für 2 bis 24 Stunden umfasst.

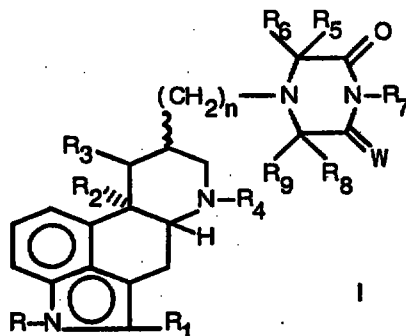
9. Verfahren nach Anspruch 8, wobei das organische Lösungsmittel Toluol, Xylol, Acetonitril, Dimethylformamid oder Dimethylsulfoxid ist.

10. Pharmazeutische Zusammensetzung, umfassend ein Ergolinderivat gemäß einem der Ansprüche 1 bis 7, ein Ergolinderivat, hergestellt gemäß einem der Ansprüche 8 bis 9, oder ein pharmazeutisch verträgliches Salz solch eines Ergolinderivates in Mischung mit einem pharmazeutisch verträglichen Streckmittel oder Träger.

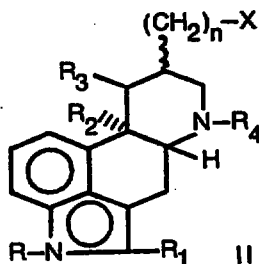
11. Verwendung eines Ergolinderivates gemäß einem der Ansprüche 1 bis 7 oder eines pharmazeutisch verträglichen Salzes davon bei der Herstellung einer pharmazeutischen Zusammensetzung mit antihypertensiver, anxiolytischer oder antipsychotischer Wirkung.

Patentansprüche für den Vertragsstaat: AT

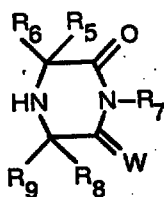
1. Verfahren zur Herstellung eines Ergolinderivates der allgemeinen Formel (I)



wobei R ein Wasserstoffatom oder eine Methylgruppe darstellt; R_1 ein Wasserstoffatom oder ein Fluoratom, ein Chloratom oder Bromatom, eine Methylgruppe oder eine Phenylthiogruppe oder eine Alkylthiogruppe mit 1 bis 4 Kohlenstoffatomen darstellt; entweder R_2 ein Wasserstoffatom oder eine Methoxygruppe und R_3 ein Kohlenwasserstoffgruppe mit 1 bis 4 Kohlenstoffatomen darstellt; entweder R_2 und R_3 zusammen eine chemische Bindung bilden; R_4 ein Wasserstoffatom darstellen, oder R_2 und R_3 zusammen eine chemische Bindung bilden; R_5 , R_6 , R_8 und R_9 unabhängig voneinander ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen, oder R_5 und R_6 wie oben definiert sind und R_8 und R_9 zusammen eine Ethylen- oder Trimethylengruppe bilden; R_7 ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Phenylgruppe oder eine Gruppe der allgemeinen Formel $NR'R''$ darstellen, wobei entweder jeder der Substituenten R' und R'' unabhängig voneinander ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder eine C_{1-5} -Alkanoyl- oder Benzoylgruppe darstellen, oder R' und R'' zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterozyklischen Ring bilden; W ein Sauerstoffatom oder zwei Wasserstoffatome darstellt; und n 0, 1 oder 2 ist; oder eines pharmazeutisch verträglichen Salzes solch eines Ergolinderivates, dadurch gekennzeichnet, dass in einem organischen Lösungsmittel in Gegenwart von Kaliumjodid oder Natriumjodid bei 80 bis 150°C für 2 bis 24 Stunden ein Ergolinderivat der allgemeinen Formel (I)



wobei R, R₁, R₂, R₃, R₄ und n wie im Anspruch 1 definiert sind und X ein Chlor- oder Bromatom oder eine Msyloxy- oder Tosyloxygruppe darstellt, mit einem Piperazinderivat der allgemeinen Formel (III)



III

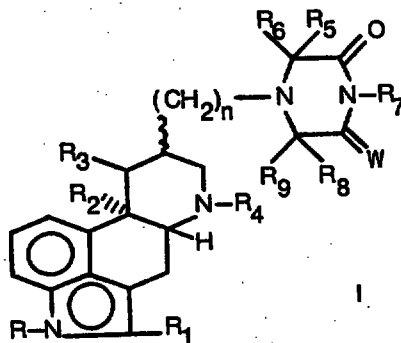
wobei R₅, R₆, R₇, R₈, R₉ und W wie oben definiert sind, kondensiert wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass das organische Lösungsmittel Toluol, Xylol, Acetonitril, Dimethylformamid oder Dimethylsulfoxid ist.

3. Verwendung einer pharmazeutischen Zusammensetzung, umfassend ein Ergolinderivat gemäß Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon bei der Herstellung einer pharmazeutischen Zusammensetzung mit antihypertensiver, anxiolytischer oder antipsychotischer Wirkung.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Derivé de l'ergoline, représenté par la formule générale (I):



dans laquelle:

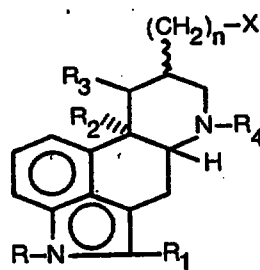
- R représente un atome d'hydrogène ou un groupe méthyle;
- R₁ représente un atome d'hydrogène ou un atome de fluor, de chlore ou de brome, un groupe méthyle ou phénylthio ou un groupe alkylthio ayant de 1 à 4 atomes de carbone;
- ou bien R₂ représente un atome d'hydrogène ou un groupe méthoxy et R₃ représente un atome d'hydrogène, ou bien R₂ et R₃ représentent ensemble une liaison chimique;
- R₄ représente un groupe hydrocarboné ayant de 1 à 4 atomes de carbone;
- ou bien R₅, R₆, R₈ et R₉ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ayant de 1 à 4 atomes de carbone, ou bien R₅ et R₈ sont tels que définis ci-dessus et R₆ et R₉ représentent ensemble un groupe éthylène ou triméthylène;
- R₇ représente un atome d'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone, un groupe phényl ou un groupe de formule générale NR'R'' dans laquelle ou bien R' et R'' représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone ou un groupe alcanoyle en C₁ à C₅ ou benzoyle, ou bien R' et R'', conjointement avec l'atome d'azote auquel ils sont liés, représentent un noyau hétérocyclique;
- W représente un atome d'oxygène ou deux atomes d'hydrogène; et
- n vaut 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable d'un tel dérivé de l'ergoline.

2. Méthyl-6 (dioxo-3,5 pipérazinyl-1 méthyl)-8β ergoline.
3. Diméthyl-1,6 (dioxo-3,5 pipérazinyl-1 méthyl)-8β ergoline.
4. Méthyl-6 (dioxo-3,5 méthyl-4 pipérazinyl-1 méthyl)-8β ergoline.
5. Méthyl-6 (dioxo-3,5 amino-4 pipérazinyl-1 méthyl)-8β ergoline.
6. Méthyl-6 didéshydro-9,10 (dioxo-3,5 pipérazinyl-1 méthyl)-8β ergoline.
7. Méthyl-6 (oxo-3 pipérazinyl-1 méthyl)-8β ergoline.

8. Procédé de préparation d'un dérivé de l'ergoline tel que défini à la revendication 1, le procédé comprenant la condensation, dans un solvant organique, en présence d'iodure de potassium ou d'iodure de sodium, à une température de 80°C à 150°C, pendant un laps de temps allant de 2 à 24 heures, d'un dérivé de l'ergoline de formule générale (II):

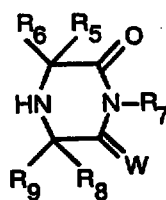




II

dans laquelle:

- R, R₁, R₂, R₃, R₄ et n sont tels que définis cidessus; et
- X représente un atome de chlore ou un atome de brome ou un groupe mésoxy ou tosyloxy, avec un dérivé de pipérazine de formule générale (III):



III

dans laquelle R₅, R₆, R₇, R₈, R₉ et W sont tels que définis à la revendication 1.

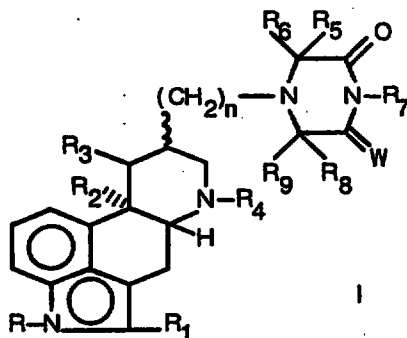
9. Procédé selon la revendication 8, dans lequel le solvant organique est le toluène, le xylène, l'acétonitrile, le diméthylformamide ou le diméthylsulfoxyde.

10. Composition pharmaceutique comprenant un dérivé de l'ergoline tel que défini à l'une des revendications 1 à 7, un dérivé de l'ergoline préparé selon l'une des revendications 8 et 9 ou un sel pharmaceutiquement acceptable d'un tel dérivé de l'ergoline, en mélange avec un diluent ou support pharmaceutiquement acceptable.

11. Utilisation d'un dérivé de l'ergoline tel que défini à l'une des revendications 1 à 7, ou d'un sel pharmaceutiquement acceptable de ce dérivé, dans la préparation d'une composition pharmaceutique ayant des activités antihypertensives, anxiolytiques ou antipsychotiques.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un dérivé de l'ergoline, représenté par la formule générale (I):



dans laquelle:

- R représente un atome d'hydrogène ou un groupe méthyle;
- R₁ représente un atome d'hydrogène ou un atome de fluor, de chlore ou de brome, un groupe méthyle ou phénylthio ou un groupe alkylthio ayant de 1 à 4 atomes de carbone;
- ou bien R₂ représente un atome d'hydrogène ou un groupe méthoxy et R₃ représente un atome d'hydrogène, ou bien R₂ et R₃ représentent ensemble une liaison chimique;
- R₄ représente un groupe hydrocarboné ayant de 1 à 4 atomes de carbone;
- ou bien R₅, R₆, R₈ et R₉ représentent chacun indépendamment un atome d'hydrogène ou un groupe



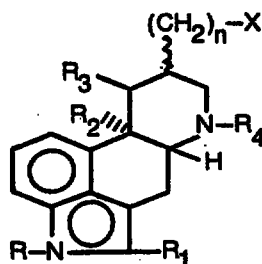
alkyle ayant de 1 à 4 atomes de carbone, ou bien R_5 et R_6 sont tels que définis ci-dessus et R_6 et R_9 représentent ensemble un groupe éthylène ou triméthylène;

— R_7 représente un atome d'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone, un groupe phényl ou un groupe de formule générale $NR'R''$ dans laquelle ou bien R' et R'' représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone ou un groupe alcanoyle en C_1 à C_5 ou benzoyle, ou bien R' et R'' , conjointement avec l'atome d'azote auquel ils sont liés, représentent un noyau hétérocyclique;

— W représente un atome d'oxygène ou deux atomes d'hydrogène; et

— n vaut 0, 1 ou 2;

ou d'un sel pharmaceutiquement acceptable d'un tel dérivé de l'ergoline, caractérisé par le fait qu'on condense, dans un solvant organique, en présence d'iodure de potassium ou d'iodure de sodium, à une température de 80°C à 150°C , pendant de 2 à 24 heures, un dérivé de l'ergoline de formule générale (II):

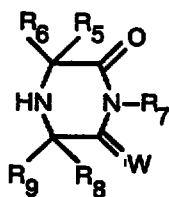


II

dans laquelle:

— R , R_1 , R_2 , R_3 , R_4 et n sont tels que définis à la revendication 1; et

— X représente un atome de chlore ou un atome de brome ou un groupe mésoxy ou tosyloxy, avec un dérivé de pipérazine de formule générale (III):



III

dans laquelle R_5 , R_6 , R_7 , R_8 , R_9 et w ont la définition cidessus.

2. Procédé selon la revendication 1, caractérisé par le fait que le solvant organique est le toluène, le xylène, l'acétonitrile, le diméthylformamide ou le diméthylsulfoxyde.

3. Utilisation d'une composition pharmaceutique comprenant un dérivé de l'ergoline tel que défini à la revendication 1, ou d'un sel pharmaceutiquement acceptable de ce dérivé, dans la préparation d'une composition pharmaceutique ayant des activités antihypertensives, anxiolytiques ou antipsychotiques.

