AU9170788

(12) PATENT ABRIDGMENT (11) Document No. AU-B-70788/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 644625

(54) Title
PROCESS FOR PREPARING ERGOLINE DERIVATIVES

International Patent Classification(s)
(51)[5] C07D 457/00 C07D 457/02

(21) Application No. : 70788/91 (22) Application Date : 21.01.91

(87) PCT Publication Number : WO91/11447

(30) Priority Data

(31) Number	(32) Date	(33) Country
9001774	25.01.90	GB UNITED KINGDOM
9025849	28.11.90	GB UNITED KINGDOM

(43) Publication Date : 21.08.91

(44) Publication Date of Accepted Application : 16.12.93

(71) Applicant(s)
FARMITALIA CARLO ERBA S.R.L.

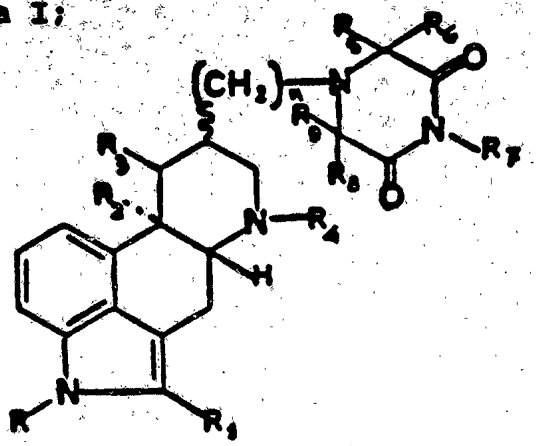
(72) Inventor(s)
SERGIO MANTEGANI; GABRIELLA TRAQUANDI; TIZIANO BANDIERA; ENZO BRAMBILLA

(74) Attorney or Agent
GRIFFITH HACK & CO , GPO Box 1285K, MELBOURNE VIC 3001

(56) Prior Art Documents
EP 197241

(57) Claim

1. A process for preparing an ergoline derivative of the formula I;

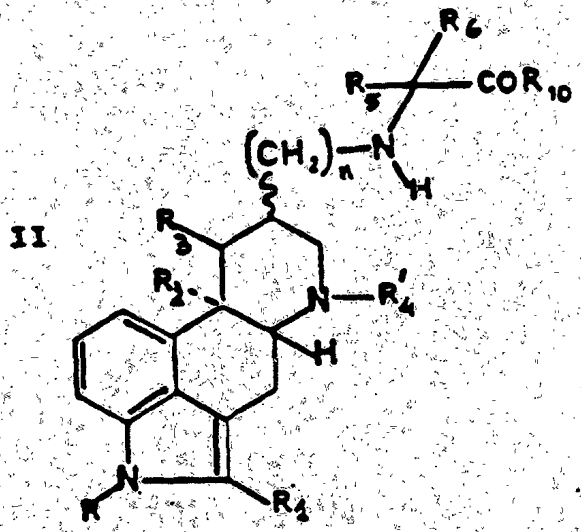


I

wherein R represents a hydrogen atom or a C_1-C_3 alkyl group; R_1 represents a hydrogen atom, chlorine, bromine atom or a methyl group; either R_2 and R_3 represent hydrogen atoms or R_2 and R_3 together represent a chemical bond; R_4 represents a hydrocarbon group having from 1 to 4 carbon atoms; each of R_5, R_6, R_8 and R_9 independently represents a hydrogen atom

.../2

or an alkyl group having from 1 to 4 carbon atoms; R_7 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a cycloalkyl group having from 3 to 7 carbon atoms and n is 0, 1 or 2, which process comprises reacting, in an organic solvent in the presence of an acid scavenger, an ergoline of the formula II with an α-halogen derivative of formula III:

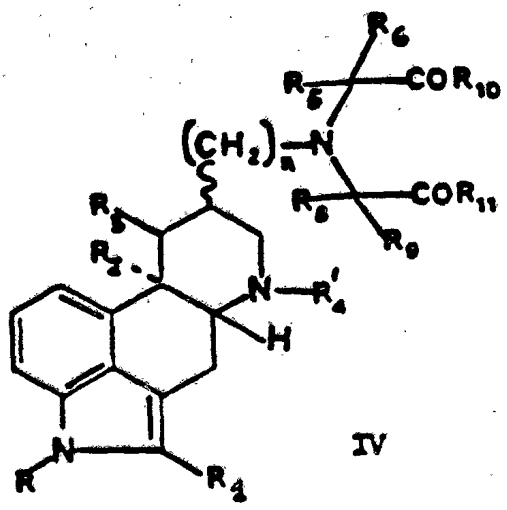


II



III

wherein n, R, R_1, R_2, R_3, R_5, R_6, R_8 and R_9 have the above given meanings, R_{10} and R_{11} independently represent a C_1-C_4 alkoxy group or an amino group NHR_7 wherein R_7 is as defined above, X represents a halogen atom, R'_4 represents a hydrocarbon group having from 1 to 4 carbon atoms or a N-protecting group and, if necessary, converting the resultant compound of the formula IV:



IV

.../3

wherein R, R_1, R_2, R_3, R_5, R_6, R_8, R_9 and n are as defined above and R'_4 is a N-protecting group into a compound of the formula IV in which R'_4 is C_1-C_4 hydrocarbon group by deprotection using a base, formic acid or Zn/dust and alkylation with a halide derivative R_4-Hal in the presence of an acid scavenger, if necessary converting the compound of the formula IV in which R_{10} and R_{11} both represent an alkoxy group into a compound of the formula IV in which R_{10} and R_{11} are both amino groups by ammonolysis; and cyclizing a said compound of the formula IV, either (i) in which R_{10} and R_{11} both represent amino groups NHR_7, wherein R_7 is as defined above by heating in a solvent at a temperature of 100-200°C, or (ii) in which R_{10} is an alkoxy group and R_{11} represents an amino group NHR_7 wherein R_7 is as defined above, by heating in vacuo at the melting point of the compound of formula IV or by hydrolysis of the COR_{10} carboxylate group and subsequent treatment with a condensing agent in a solvent at a temperature of from 50° to 150°C.

OPI DATE 21/08/91 APPLN. ID 70788 / 91

PCT AOJP DATE 03/10/91 PCT NUMBER PCT/EP91/00104

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 457/02 — A1

(11) International Publication Number: WO 91/11447

(43) International Publication Date: 8 August 1991 (08.08.91)

(21) International Application Number: PCT/EP91/00104

(22) International Filing Date: 21 January 1991 (21.01.91)

(30) Priority data:

9001774.0	25 January 1990 (25.01.90)	GB
9025849.2	28 November 1990 (28.11.90)	GB

(71) Applicant *(for all designated States except US)*: FARMITALIA CARLO ERBA S.R.L. [IT/IT]; Via Carlo Imbonati, 24, I-20159 Milan (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : MANTEGANI, Sergio [IT/IT]; Via Carlo Pisacane, 57, I-20129 Milan (IT). TRAQUANDI, Gabriella [IT/IT]; Via Cilea, 106, I-20151 Milan (IT). BANDIERA, Tiziano [IT/IT]; Cors Vittorio Emanuele, 44, I-27025 Gambolo (IT). BRAMBILLA, Enzo [IT/IT]; Via Togliatti, 41/b, I-22066 Mariano Comense (IT).

(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

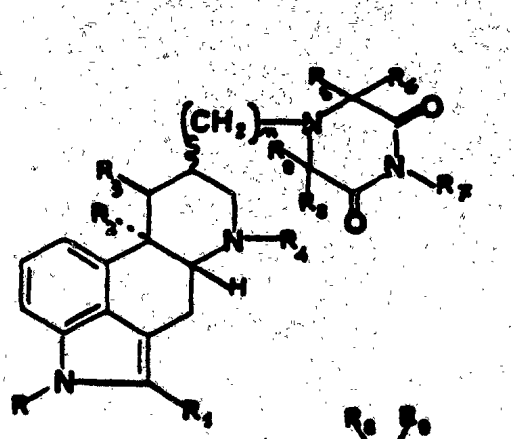
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU, US.

Published

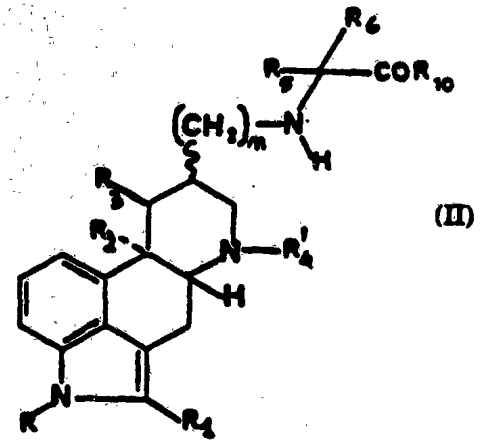
With international search report.

614625

(54) Title: PROCESS FOR PREPARING ERGOLINE DERIVATIVES



(I)



(II)



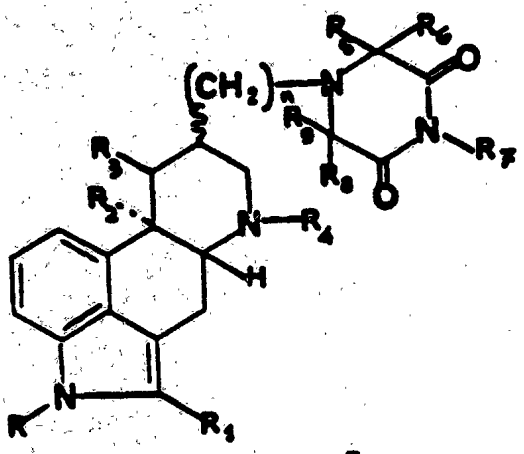
(III)

(57) Abstract

Ergoline derivatives of formula (I), wherein R represents hydrogen or C_1-C_4 alkyl; R_1 represents hydrogen, chlorine, bromine or methyl; either R_2 and R_3 both represent hydrogen or together represent a chemical bond; R_4 represents a C_1-C_4 hydrocarbon group; each of R_5, R_6, R_8 and R_9 independently represents hydrogen or C_1-C_4 alkyl; R_7 represents hydrogen, C_1-C_4 alkyl, phenyl or C_3-C_7 cycloalkyl and n is 0, 1 or 2; are prepared by reaction between compounds of formulae (II) and (III), and subsequent cyclization of the resultant compounds. The compounds of formula (I) are known useful anxiolytic, antipsychotic and anti-parkinson agents.

PROCESS FOR PREPARING ERGOLINE DERIVATIVES

The present invention provides a process for the preparation of known ergoline derivatives having the formula I:



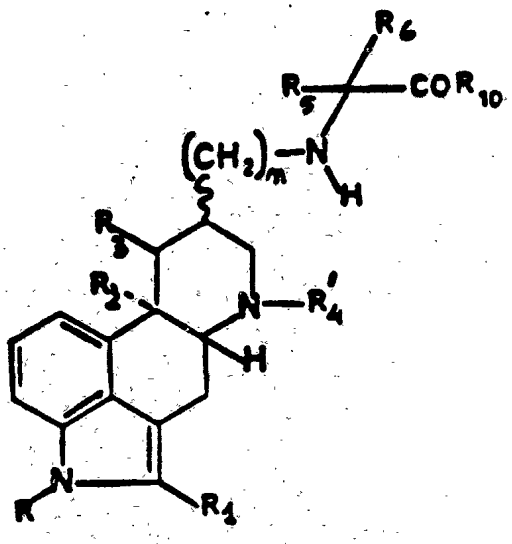
I

wherein R represents a hydrogen atom or a C_1-C_3 alkyl group; R_1 represents a hydrogen, chlorine or bromine atom or a methyl group; either R_2 and R_3 represent hydrogen atoms or R_2 and R_3 together represent a chemical bond; R_4 represents a hydrocarbon group having from 1 to 4 carbon atoms; each of R_5, R_6, R_8 and R_9 independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; R_7 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a cycloalkyl group having from 3 to 7 carbon atoms and n is 0, 1 or 2.

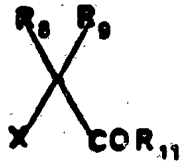
In the definition of R_4, a hydrocarbon group having from 1 to 4 carbon atoms is intended to include alkyl, cycloalkyl and unsaturated (both ethylenically and acetylenically) groups.

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

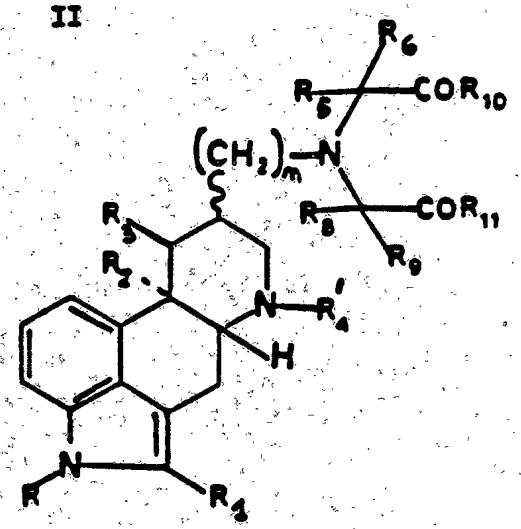
The invention provides a process comprising (i) reacting an ergoline of the formula II with α-halogen derivatives of formula III to afford ergoline derivatives of formula IV



II



III



IV

wherein n, R, R_1, R_2, R_3, R_5, R_6, R_8 and R_9 have the above given meanings, R_{10} and R_{11} are independently C_1-C_4 alkoxy group or an amino group NH-R_7 wherein R_7 is as above defined, X is a halogen atom; and R_4 represents a hydrocarbon group having from 1 to 4 carbon atoms or an N-protecting group;

(ii) if R'_4 is an N-protecting group in the resultant compound of the formula IV, converting the said compound by deprotection using a base, formic acid or Zn/dust and alkylation with a halide derivative R_4-Hal in the presence of an acid scavenger into a corresponding

AUSTRALIA PATENT OFFICE

compound of the formula IV in which R'_4 is a C_1-C_4 hydrocarbon group;

(iii) if R_{10} and R_{11} both represent alkoxy groups in the resultant compound of formula IV, converting the said compound by ammonolysis into a corresponding compound of formula IV in which R_{10} and R_{11} are both amino groups; and

(iv) cyclising a said compound of formula IV, either (i) in which R_{10} and R_{11} both represent amino groups NHR_7, wherein R_7 is as defined above, by heating in a solvent at a temperature of 100°C to 200°C, or (ii) in which R_{10} is an alkoxy group and R_{11} represents an amino group NHR_7 wherein R_7 is as defined above, by heating in vacuo at the melting point of the compound of formula IV or by hydrolysis of the COR_{10} carboxylate group and subsequent treatment with a condensing agent in a solvent a temperature of from 50°C to 150°C.

A C_1-C_4 alkoxy group may be, for example, an ethoxy or methoxy group. A halogen may be chlorine or bromine. An N-protecting group may, for example, be an acetyl, tert-butyloxycarbonyl or trichloroethyloxycarbonyl group.

The wavy line (~~~) in formulae I, II and IV indicates that the substituent in the 8-position may be in the α-configuration, i.e. below the plane of the ring, in the β-configuration, i.e. above the plane of the ring, or in both, i.e. a mixture of derivatives of formula I, II or IV is present with some having the substituent in the 8-position in the α-configuration and the rest having the substituent in the 8-position in the β-configuration (a diastereoisomeric mixture).

The condensation process (i) is carried out in an organic solvent such as toluene, acetonitrile, or dimethylformamide in presence of an acid scavenger such as an inorganic carbonate or triethylamine. When the reaction is complete the solvent is removed and the residue is purified by crystallization or chromatography according to well known techniques.

AUSTRALIA PATENT OFFICE

The compounds of formula IV in which R'_4 is a N-protecting group are preferred starting compounds when n is 1 and the substituent in the 8-position is in the α-configuration.

If necessary, a compound of formula IV in which R_{10} and R_{11} are both alkoxy groups may be converted into another compound of the formula IV in which R_{10} and R_{11} are both amino groups by ammonolysis in a suitable solvent such as methanol, ethanol or dimethylformamide.

According to the present invention, the intermediate derivatives of formula IV are then cyclized to give the derivatives of formula I. In particular, when R_{10} and R_{11} are both amino groups the cyclization may suitably be accomplished by heating in a solvent such as phenol, xylenol or cresol.

When R_{10} is an alkyloxy group and R_{11} is an amino group NH-R_7 the cyclization to give an ergoline derivative of the formula I is carried out by heating in vacuo at the melting point of the compound of formula IV or by the hydrolysis of the COR_{10} group and subsequent treatment with a suitable condensing agent such as acetic anhydride, alkylchlorocarbonate or diimidazolcarbonyl in a solvent such as tetrahydrofuran, 1,4-dioxane or dimethylformamide within the range of temperature of from 50°-150°C.

The starting compounds of formulae II and III which are employed in the process according to the invention are known compounds or may be prepared by established procedures starting from known compounds. For example, the compounds of the formula II and their preparation are described in our EP-A-0126968.

The compounds of formula I and their pharmaceutically acceptable salts are useful anxiolytic, antipsychotic and anti Parkinson agents, as described in

EP-A-197,241, US-A-4,847,253 and WO 90/04396.
The ergoline derivatives of formula I prepared by the present process may therefore be formulated as a pharmaceutical composition. The composition also comprises a pharmaceutically acceptable carrier or diluent.

The preparation of compounds of general formula I is described in the above cited EP-A-0197,241. Although the process there described is capable of producing derivatives of the general formula I, the process here described is more versatile allowing the synthesis of a higher number of derivatives of general formula I especially when R_2 and R_3 together represent a chemical bond.

The following Examples illustrate the invention.

EXAMPLE 1

1-Phenyl-4-(6-methyl-9,10-ergolen-8β-yl)-methylpiperazin-2,6-dione.

A solution of 5.08 g (0.015 m) of N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester and 1.03 g (0.0075 m) of potassium carbonate and 3.85 g (0.018 m) of N-phenylbromo-acetamide in 200 ml of dimethylformamide was stirred at 50°C for 4 hours.

The resulting solution was poured into brine and the precipitate was extracted with ethyl acetate. Removal of the solvent and crystallization from ethanol afforded 6.5 g of N-phenylcarbamoylmethyl-N-[(6-methyl-9,10-ergolen-8β-yl)-methyl]-glycine ethyl ester m.p. 196°-197°C.

A solution of 6.5 g (0.013 m) of this ester in 50 ml of ethanol was tested with 17.9 ml of sodium hydroxide 1M and the resulting solution was heated at 80°C for 30 minutes. After acidification with 179 ml of hydrochloric acid 1M, the resulting solution was poured into ice water. The precipitate was filtered off and then washed with water, acetone and dried giving 5.1 g of N-phenylcarbamoylmethyl-N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine. m.p. 252°-255°C. To a suspension of 5 g (0.011 m) of N-

phenylcarbamoylmethyl-N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine in 50 ml of anhydrous dioxane was added portionwise 1.96 g (0.121 m) of N,N'-diimidazole carbonyl. The resulting solution was refluxed for 3 hours. After removal of the solvent, the residue was poured into chloroform and extracted with a 10% ammonium hydroxide solution. The organic phase was washed with brine and after drying evaporated to dryness. After crystallization from acetone, 4.1 g of the title compounds were obtained m.p. 240°-245°C.

EXAMPLE 2

4-(6-Methyl-9,10-ergolen-8β-yl)methylpiperazin-2,6-dione

Operating as in Example 1, but employing bromoacetamide in place of N-phenylbromoacetamide, N-carbamoylmethyl-N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester was obtained m.p. 172°-174°C. From this N-carbamoylmethyl-N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine was obtained m.p. 242°-243°C. Finally the title compound was obtained in 75% yield m.p. 224°-225°C.

EXAMPLE 3

4-(1,6-Dimethyl-9,10-ergolen-8β-yl)methylpiperazin-2,6-dione

Operating as in Example 2, but employing N-[(1,6-dimethyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester in the place of N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester, N-carbamoylmethyl-N-[(1,6-dimethyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester was obtained m.p. 180°-183°C. From this N-carbamoylmethyl-N-[(1,6-dimethyl-9,10-ergolen-8β-yl)methyl]-glycine was obtained. m.p. and finally the title compound was obtained in 55% yield m.p. 216°-218°C.

EXAMPLE 4

4-(2-Bromo-6-methyl-9,10-ergolen-8β-yl)methylpiperazin-2,6-dione

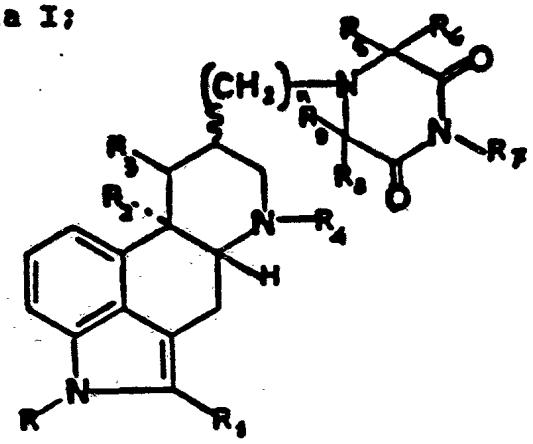
Operating as in Example 1, but employing ethyl bromoacetate in place of N-phenylbromoacetamide, and N-[(2-bromo-6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester in place of N-[(6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester, N-ethoxycarbonylmethyl-N-[(2-bromo-6-methyl-9,10-ergolen-8β-yl)methyl]-glycine ethyl ester was obtained m.p. 93°-96°C.

A solution of 10 g of this ester in 100 ml of methanol saturated with gaseous ammonia was aged at room temperature for 24 hours. Concentration mixture afforded N-carbamoyl methyl-N-[(2-bromo-6-methyl-9,10-ergolen-8β-yl)methyl]-glycine amide in 85% yield m.p. 218°-221°C.

A mixture of 5 g of N-carbamoylmethyl-N-[(2-bromo-6-methyl-9,10-ergolen-8β-yl)methyl]glycinamide and 30 g of phenol was heated under nitrogen at 160°C for 30 minutes. After cooling, the reaction mixture was taken up in diethyl ether and the precipitate was crystallized twice from acetone affording 3.9 g of the title compound m.p. 242°-245°C.

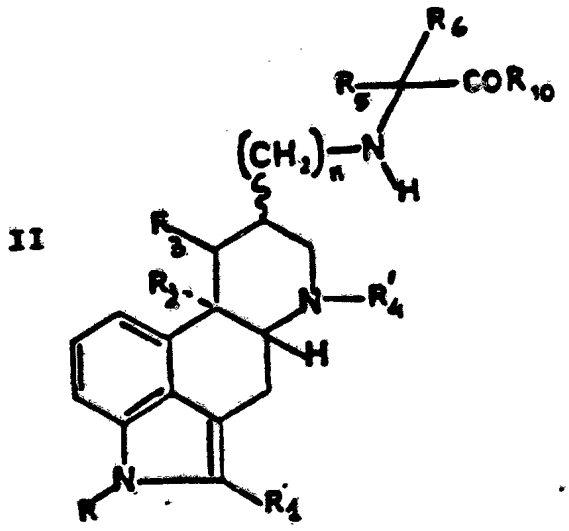
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for preparing an ergoline derivative of the formula I;

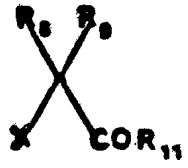


I

wherein R represents a hydrogen atom or a C_1-C_3 alkyl group; R_1 represents a hydrogen atom, chlorine, bromine atom or a methyl group; either R_2 and R_3 represent hydrogen atoms or R_2 and R_3 together represent a chemical bond; R_4 represents a hydrocarbon group having from 1 to 4 carbon atoms; each of R_5, R_6, R_8 and R_9 independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; R_7 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a phenyl group or a cycloalkyl group having from 3 to 7 carbon atoms and n is 0, 1 or 2, which process comprises reacting, in an organic solvent in the presence of an acid scavenger, an ergoline of the formula II with an α-halogen derivative of formula III:

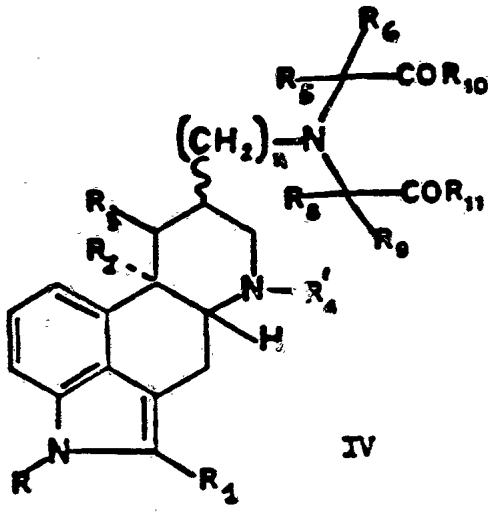


II



III

wherein n, R, R_1, R_2, R_3, R_5, R_6, R_8 and R_9 have the above given meanings, R_{10} and R_{11} independently represent a C_1-C_4 alkoxy group or an amino group NHR_7 wherein R_7 is as defined above, X represents a halogen atom, R'_4 represents a hydrocarbon group having from 1 to 4 carbon atoms or a N-protecting group and, if necessary, converting the resultant compound of the formula IV:



IV

wherein R, R_1, R_2, R_3, R_5, R_6, R_8, R_9 and n are as defined above and R'_4 is a N-protecting group into a compound of the formula IV in which R'_4 is C_1-C_4 hydrocarbon group by deprotection using a base, formic acid or Zn/dust and alkylation with a halide derivative R_4-Hal in the presence of an acid scavenger, if necessary converting the compound of the formula IV in which R_{10} and R_{11} both represent an alkoxy group into a compound of the formula IV in which R_{10} and R_{11} are both amino groups by ammonolysis; and cyclizing a said compound of the formula IV, either (i) in which R_{10} and R_{11} both represent amino groups NHR_7, wherein R_7 is as defined above by heating in a solvent at a temperature of 100-200°C, or (ii) in which R_{10} is an alkoxy group and R_{11} represents an amino group NHR_7 wherein R_7 is as defined above, by heating in vacuo at the melting point of the compound of formula IV or by hydrolysis of the COR_{10} carboxylate group and subsequent treatment with a condensing agent in a solvent at a temperature of from 50°

AUSTRALIA PATENT OFFICE

to 150°C.

2. A process according to claim 1 wherein, in the reaction between the compounds of the formulae II and III, the organic solvent is toluene, acetonitrile or dimethylformamide and the acid scavenger is an inorganic carbonate or triethylamine.

3. A process according to claim 1 or 2 in which the solvent used in the step of cyclising a compound of formula IV in which R_{10} and R_{11} both represent amino groups is phenol, xylenol or cresol.

4. A process according to claim 1 or 2 in which the condensing agent used in the step of cyclising a compound of formula IV in which R_{10} is an alkoxy group and R_{11} is an amino group NHR_7 is acetic anhydride, alkylchlorocarbonate or diimidazolcarbonyl and the solvent is tetrahydrofuran, 1,4-dioxane or dimethylformamide.

5. A process for preparing an ergoline derivative, the process being substantially as hereinbefore described in any one of Examples 1 to 4.

DATED this 14th day of October 1993

FARMITALIA CARLO ERBA S.r.l.
By Their Patent Attorneys

GRIFFITH HACK & CO
Fellows Institute of Patent
Attorneys of Australia

AUSTRALIA PATENT OFFICE

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00104

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 457/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP, A1, 0197241 (FARMITALIA CARLO ERBA S.P.A.) 15 October 1986, see the whole document --	1-8
Y	Chem. Ber. vol. 52, 1919, J.W. Dubsky et al: "Zur Kenntnis der Diketo-piperazine" pages 221-234, see especially pages 226-228 --	1-8
Y	Chemical Abstracts, volume 70, no. 9, 3 March 1969, (Columbus, Ohio, US), B.P. Das et al.: "Formation of 2,6-dioxopiperazine derivatives in the reaction between β-phenylethylamine and ethyl chloroacetate", see page 353, abstract 37782c, & Indian J. Chem. 1968, 6(3), 170- 172 --	1-8

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th April 1991	13. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	J. Org. Chem., vol. 50, 1985, M. Harfenist et al: "Enantiospecific Synthesis of the trans-9-[3-(3,5--Dimethyl-1-piperazinyl)propyl]carbazoles", pages 1356-1359, see scheme I --	1-8
Y	EP, A1, 0126968 (FARMITALIA CARLO ERBA S.P.A.) 5 December 1984, see examples 6, 12 and 14 --	1-8

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/EP 91/00104

SA 43694

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 23/03/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0197241	15/10/86	AU-B-	581280	16/02/89
		AU-D-	5226086	24/07/86
		CA-A-	1243670	25/10/88
		JP-A-	61167686	29/07/86
		SU-A-	1500160	07/08/89
		US-A-	4728649	01/03/88
EP-A1- 0126968	05/12/84	AU-B-	556968	27/11/86
		AU-D-	2742184	01/11/84
		CA-A-	1205801	10/06/86
		DE-A-	3475709	26/01/89
		JP-C-	1466858	10/11/88
		JP-A-	59206382	22/11/84
		JP-B-	63013996	29/03/88
		SU-A-	1327788	30/07/87
		US-A-	4690929	01/09/87