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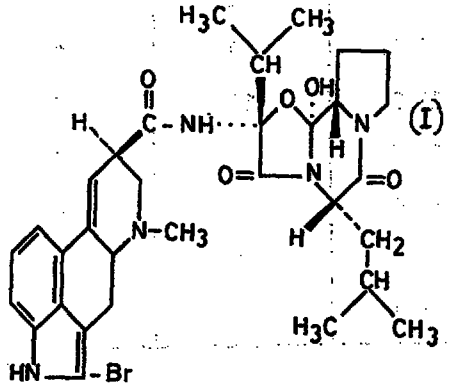
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(54) BROMO-ERGOCRYPTINE

(71) We, SANDOZ LTD., of 35 Lichtstrasse 4000 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 2 - bromo - α - ergocryptine of formula I,



(I)

and acid addition salts thereof.

2 - Bromo - α - ergocryptine and its acid addition salts may be obtained in accordance with the invention by brominating ergocryptine in a solvent, which is inert under the reaction conditions, with a mild brominating agent, e.g. N-bromophthalimide, N-bromosuccinimide or N-bromocaprolactam, purifying the resulting 2 - bromo - α - ergocryptine in manner known *per se* and then optionally converting it into its acid addition salts.

Suitable brominating agents are amides or imides, brominated on the nitrogen atom, of aliphatic or aromatic carboxylic or sulphonic acids, e.g. N-bromophthalimide, N-bromosuccinimide or N-bromocaprolactam (1 to 3 mols) or a bromo-dioxane complex (0.5 mols Br_2).

Bromination is conveniently effected in an inert, polar solvent, e.g. dioxane, acetonitrile or methylene chloride, at a temperature between 10 and 80°C.

Purification of the resulting crude 2 - bromo - α - ergocryptine may be effected in conventional manner, e.g. by chromatography and/or recrystallization.

2 - Bromo - α - ergocryptine is a crystalline substance at room temperature and forms stable salts, which are crystalline at room temperature, with organic or inorganic acids. Examples of acids which may be used for salt formation are inorganic acids, such as hydrochloric, hydrobromic or sulphuric acid, or organic acids, such as oxalic, tartaric or methanesulphonic acid.

2 - Bromo - α - ergocryptine and its pharmaceutically acceptable acid addition salts inhibit the secretion of luteotropic hormone (prolactin) and are useful because of their antifertility properties, which differ from similar representatives of the ergotoxine group, e.g. α-ergocryptine or ergocornine, in that

1. their effect is more specific, and
2. they are better tolerated.

2 - Bromo - α - ergocryptine and its pharmaceutically acceptable acid addition salts exhibit the above-mentioned properties at daily dosages ranging from about 0.6 milligrams to about 2.5 milligrams per kilogram animal body weight. However, for larger mammals, suitable daily doses range from about 2 to about 20 mg, in view of the specificity of action.

The properties of 2 - bromo - α - ergocryptine indicated above may be ascertained as follows:

1. *Antifertility effect.*

Each of two fertile female rats (control and test animal) is placed with an experienced male rat in a cage for a period of 19 days. The test preparation or pure solvent is injected subcutaneously to the female rats on the 5th, 10th and 15th day of the test. During the autopsy on the 19th day the uterine horns are examined under a magnifying glass for implantations and resorptions. Each dose group consists of 11 test animals and the same number of control animals. Evaluation of the test is effected by making the fertility of the test animals equivalent to 100% and expressing the fertility decrease of the test animals as a percentage. These tests are repeated with different doses in order to ascertain the relationship between dose and effect and to determine an ED_{50}.

Table I gives a summary of the results of such a test series. An ED_{50} of 0.75 mg/kg may be calculated from the fertility inhibition values in accordance with the test method of Litchfield and Wilcoxon, J. Pharmacol. *96*, 99 (1949).

TABLE I

Dose mg/kg	anti-fertility effect %	number of fetus for every pregnant animal		number of resorptions	
		V	K	V	K
0.25	0	10.3	10.3	5	8
0.5	0	10.9	11.3	8	10
0.65	40	11.2	10.4	4	8
0.75	50	12.2	9.3	0	9
0.85	55	11.6	11.3	11	6
1.0	80	12.0	10.7	3	9
1.25	91	12.0	10.6	1	4
2.5	100	—.—	10.9	0	3
20.0	100	—.—	11.2	0	9

V: test animals, K: control animals.

2. *Determination of the specificity of the antifertility effect.*

In what follows the quantitative ratios of implantation inhibition and lactation inhibition of 2 - bromo - α - ergocryptine are examined and compared with those of α-ergocryptine.

The method used for determining lactation inhibition is as follows:

Each of a number of female rats having a body weight of 180—200 g is placed together with a breeding male. About 18—19 days later, i.e. shortly before the births, the pregnant female animals were individually placed in fresh tubs. Only 8 young animals of a brood were left with the mother animals. The broods were weighed with the exactness of 1 gram beginning from the first day in the morning. The test substance was injected subcutaneously to the lactating mother animal on the 6th, 7th or 8th day after birth of the young animals, in the evening. The next day the broods were weighed in the morning and in the evening and on the following days only in the morning.

Evaluation of the dose-effect relationship:

Young animals from control broods, the mother animals of which were only treated with solvent, show an average % weight increase from the day of the injection to the morning of the following day of 100% to 114.2%. The difference of 14.2% gives the standard for determining lactation inhibition. An average % weight increase of a young animal from the morning of the injection day to the first weighing the following morning of 14.2% is defined as a *lactation inhibition of 0%*. Therefore, a

weight increase of only 7.1% is considered as a 50% lactation inhibition and a complete stagnation of weight development during the period in question is considered as a *100% lactation inhibition.*

The results obtained with 2 - bromo - α - ergocryptine and α-ergocryptine are indicated in the following Table II.

TABLE II

2-bromo-α-ergocryptine		α-ergocryptine	
Dose mg/kg	Lactation inhibition %	Dose mg/kg	Lactation inhibition %
0.33	14	—.—	—.—
0.50	24	0.60	58
0.75	28	—.—	—.—
1.10	29	—.—	—.—
1.70	46	1.15	71
2.50	40	1.50	69
3.80	45	2.1	89

As has already been indicated in Table I, 2 - bromo - α - ergocryptine exerts a fertility inhibition which is strongly dependent on the dose. The compound also inhibits lactation, depending on the dose. It is surprising, however, that the relationship dose: effect of lactation inhibition progresses more slowly than fertility inhibition. The values for the ED_{50} are therefore different. After repeated tests the ED_{50} for fertility inhibition is 0.7 to 0.8 mg/kg s.c., and for lactation inhibition about 3.5 mg/kg s.c. or higher. It is therefore possible to obtain an almost complete implantation inhibition with doses that only slightly impair the milk supply of the young animals. In other words, the two effects of 2 - bromo - α - ergocryptine, i.e. implantation and lactation inhibition, show very different dose dependencies.

As opposed to this, the dose dependency of fertility inhibition and lactation inhibition in the case of α-ergocryptine is very similar. In the case of α-ergocryptine a dose which exerts a complete implantation inhibition also inhibits lactation completely.

2 - Bromo - α - ergocryptine, however, shows a specific implantation inhibiting effect in rats.

3. *Tolerance*

a) *Acute toxicity*

The LD_{50} (dose for a 50% mortality) on oral or intravenous administration was determined in tests with rabbits. The observation time after a single administration of the compound covered a period of 7 days. The results may be seen in Table III, which also contains the comparison data for α-ergocryptine.

TABLE III

Preparation	LD_{50} mg/kg rabbits	
	oral	i.v.
2-bromo-α-ergocryptine	>1000	12.0
α-ergocryptine	—	0.95

b) *Emetic effect*

Waking dogs react to parenterally administered ergot alkaloids at a certain dose range with vomiting; this may be interpreted as a central nervous effect of these peptide alkaloids. This vomiting may be released by slow i.v. administration of ergotamine with an ED_{50} of 2.5 μg/kg. α-Ergocryptine shows a similar activity; the ED_{50} is 2.6 μg/kg. 2 - Bromo - α - ergocryptine also has an emetic effect, but its ED_{50} is 7.5 μg/kg. Therefore, 2 - bromo - α - ergocryptine has an emetic effect which is 2.8 times lower than that of α-ergocryptine and 3 times lower than that of ergotamine.

The vasotonic effect of 2 - bromo - α - ergocryptine is also weak as compared with that of known, natural or partially synthetically obtained ergot alkaloids.

2 - Bromo - α - ergocryptine may be used as pharmaceutical on its own or in the form of appropriate medicinal preparations for enteral or parenteral administration. In order to produce suitable medicinal preparations the compound may be combined with inorganic or organic adjuvants which are pharmacologically inert. Examples of such adjuvants are:

for tablets and dragées:	lactose, starch, talcum and stearic acid;
for syrups:	solutions of cane sugar, invert sugar and glucose;
for injectable solutions:	water, alcohols, glycerin and vegetable oils;
for suppositories:	natural or hardened oils and waxes.

The preparations may furthermore contain suitable preserving, stabilizing and wetting agents, solubilizers, sweetening and colouring agents and flavourings.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade and are corrected.

EXAMPLE 1:

2 - Bromo - α - ergocryptine.

A solution of 3.4 g of N-bromosuccinimide in 60 cc of absolute dioxane is added dropwise in the dark, during the course of 5 minutes, to a stirred solution, heated to 60°, of 9.2 g of ergocryptine in 180 cc of absolute dioxane. The reaction mixture is stirred at this temperature for 70 minutes and is concentrated to a syrup-like consistency in a rotary evaporator at a bath temperature of 50°. The reaction mixture is subsequently diluted with 300 cc of methylene chloride, is covered with a layer of about 200 cc of a 2N sodium carbonate solution in a separating funnel and is shaken thoroughly. The aqueous phase is extracted thrice with 100 cc amounts of methylene chloride. The combined organic phases are washed once with 50 cc of water, are dried over sodium sulphate and the solvent is removed under a vacuum.

The resulting brown foam is chromatographed on a 50-fold quantity of aluminium oxide of activity II—III with 0.2% ethanol in methylene chloride as eluant, whereby the compound indicated in the heading is eluted immediately after a secondary fraction which migrates somewhat more rapidly than the fractions containing the heading compound. The last fractions to leave the aluminium oxide contain varying amounts of starting material together with the heading compound, and may be subjected directly, as mixed fractions, to an afterbromination in accordance with the method described above. The fractions containing the pure heading compound are combined and crystallized from methyl-ethyl ketone/isopropyl ether. Melting point 215—218° (decomp.), $[\alpha]_D^{20} = -195°$ (c = 1, methylene chloride). Paper chromatographic identification:

Stationary phase:	25% formamide
Mobile phase:	ether/carbon tetrachloride (1:1)
Rf values:	2 - bromo - α - ergocryptine 0.88
	α-ergocryptine 0.70

Methane sulphonate:

From methyl-ethyl ketone. Melting point 192—196° (decomposition), $[\alpha]_D^{20} = +95°$ (c = 1, methano): methylene chloride = 1:1).

EXAMPLE 2:

2 - Bromo - α - ergocryptine.

A solution of 9.2 g of ergocryptine in 200 cc of absolute dioxane is combined with a solution of 5.1 g of N-bromo-caprolactam in 300 cc of dioxane and the resulting dark reaction mixture is stirred at room temperature for 6 hours. The reaction mixture is concentrated by evaporation and is then worked up as indicated in Example 1. The resulting foam is chromatographed on a 50-fold quantity of silica gel with 3% of ethanol in methylene chloride as eluant. The compound of the heading is immediately obtained in pure form. The physical data of this compound agree with those indicated in Example 1.

EXAMPLE 3:

2 - Bromo - α - ergocryptine.

A solution of 92.5 mg of ergocryptine in 2 cc of absolute dioxane is combined with a solution of 43.4 mg of N-bromophthalimide in 2 cc of dioxane and the resulting dark reaction mixture is stirred at room temperature for 6 hours. The reaction mixture is concentrated by evaporation and is then worked up as indicated in Example 1. The resulting foam is chromatographed on a 50-fold quantity of silica gel with 3% of ethanol in methylene chloride as eluant. The title compound is immediately obtained in pure form. The physical data of this compound agree with those indicated in Example 1.

EXAMPLE 4:

2 - Bromo - α - ergocryptine.

A solution of 922 mg of ergocryptine in 18 cc of absolute dioxane is combined with a solution of 0.04 cc of Br_2 in 6 cc of dioxane and the resulting dark reaction mixture is stirred at room temperature for 2 hours. The reaction mixture is concentrated by evaporation and is then worked up as indicated in Example 1. The resulting foam is chromatographed on a 50-fold quantity of silica gel with 3% of ethanol in methylene chloride as eluant. The title compound is immediately obtained in pure form. The physical data of this compound agree with those indicated in Example 1.

WHAT WE CLAIM IS:—

1. A process for the production of 2 - bromo - α - ergocryptine or an acid addition salt thereof, which comprises brominating ergocryptine with a mild brominating agent, in a solvent which is inert under the reaction conditions and, when an acid addition salt is required, salifying.

2. A process as claimed in Claim 1, wherein the bromination is effected with N-bromophthalimide, N-bromosuccinimide, N-bromocaprolactam or a bromo-dioxane complex.

3. A process as claimed in either of the preceding Claims, wherein the solvent is dioxane, acetonitrile or methylene chloride.

4. A process as claimed in any one of the preceding Claims, wherein the bromination is carried out at a temperature between 10° and 80°C.

5. A process for the production of 2 - bromo - α - ergocryptine or an acid addition salt thereof, substantially as herein described, with reference to any one of the Examples 1 to 4.

6. 2 - Bromo - α - ergocryptine or an acid addition salt thereof, whenever produced by the process claimed in any of the preceding Claims.

7. 2 - Bromo - α - ergocryptine.

8. An acid addition salt of 2 - bromo - α - ergocryptine.

9. 2 - Bromo - α - ergocryptine methane sulphonate.

10. A pharmaceutical composition comprising 2 - bromo - α - ergocryptine or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable diluent or carrier.

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7. 2 - Bromo - α - ergocryptine.

8. An acid addition salt of 2 - bromo - α - ergocryptine.

9. 2 - Bromo - α - ergocryptine methane sulphonate.

10. A pharmaceutical composition comprising 2 - bromo - α - ergocryptine or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable diluent or carrier.

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