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PATENT SPECIFICATION

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(54) A PROCESS FOR BROMINATING α -ERGOCRYPTINE

(71) We, LEK TOVARNA FARMACEVTSKIH IN KEMICNIH IZDELKOV N.SOL.O., a Yugoslavian Body Corporate, of Celovska 135, Ljubljana, Yugoslavia, 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 a process for brominating α -ergocryptine to produce 2-bromo- α -ergocryptine.

2-Bromo- α -ergocryptine is a known compound inhibiting the secretion of the hormone prolactin and of the growth hormone. It is therapeutically applied in the treatment of amenorrhagalactorrhea (Del Pozo et al., J. Clin. Endocrinol. Metab., 38:910, 1974) and of acromegaly (A. Liuzzi et al., J. Clin. Endocrinol. Metab., 38:910 1974). As inhibitor for prolactin it advantageously affects those types of cancer, above all breast cancer, in which the activation and reactivation depend on prolactin (R. W. Turkington, L. E. Underwood and J. J. Van Wyk, N. Engl. M. Med., 285 (1971) 707). It stimulates dopamine receptors in the central nervous system and is efficacious in the treatment of Parkinson's disease (D. B. Caine et al., Brit. Med. 4 (1974) 442).

The first process for preparing 2-bromo-derivatives of ergotalkaloids was described by F. Troxler and A. Hofman in Helv. Chim. Acta 40 (1957) 2160. In Swiss Patent Specification No. 507 249, as brominating agents for ergocryptine there are cited N-bromosuccinimide, N-bromocaprolactan, N-bromophthalimide and elementary bromine in dioxane. In spite of considerable excess of brominating agent, however, the reaction is neither selective nor quantitative. Owing to the great sensitivity of ergocryptine, side-reactions can occur so that a considerable part of the starting substance decomposes to dark coloured,

partly resinous unidentified products. Also a part of the starting substance may remain unreacted.

An object of the process according to the present invention is the use of a milder and more selective brominating agent in the presence of a free radical initiator. As this reaction proceeds according to a free radical mechanism, it is made easier by compounds which can form free radicals.

According to the present invention there is provided a process for the preparation of a 2-bromo- α -ergocryptine, which process comprises brominating α -ergocryptine by the use of pyrrolidinone hydrotribromide or N-bromosaccharin in the presence of a free radical initiator.

The preferred process according to the present invention for preparing 2-bromo- α -ergocryptine is characterised in that α -ergocryptine in an inert atmosphere is brominated with pyrrolidinone hydrotribromide or N-bromosaccharin in solution in a cyclic ether in the presence of a radical initiator at room temperature.

As the cyclic ether there can be used e.g. tetrahydrofuran, tetrahydropyran or dioxane. The preferred cyclic ether is dioxane. The reaction in acetonitrile or chloroform is less selective. As the radical initiator there can be used 2,2'-azo-bis-(2-methyl-propionitrile) (G. Bianchi and P. Grunanger, Tetrahedron Letters 21 (1965) 817).

At room temperature, the reaction may be completed with stirring.

For the inert atmosphere any inert gas can be used, e.g. nitrogen.

The reaction is usually carried out by adding the brominating agent and the radical initiator to a solution of α -ergocryptine in a cyclic ether, with stirring in an inert atmosphere. The degree of formation of side-products in the course of this reaction is small, being considerably smaller than with other known brominating agents.

It is preferred that for each mole of alpha-ergocryptine 1 to 1.2 moles of brominating agent are used.

All starting substances mentioned are described in the literature and are normally available on the market.

2-Bromo-alpha-ergocryptine may be isolated from the reaction mixture by separation by chromatography using a column filled with microporous glass carrier, e.g. glass CPG-75 with 200-400 mesh and pore diameter of about 69A a product of Electro Nucleonics, Fairfield, New Jersey, USA, Chloroform can be used as the eluting agent.

From the eluate, after evaporation of the solvent and after crystallisation from diisopropylether, there is obtained pure 2-bromo-alpha-ergocryptine.

2-Bromo-alpha-ergocryptine is a less polar compound than alpha-ergocryptine. On a silica gel plate Merck (registered Trade Mark) 60 upon development with mobile phase of chloroform/methanol 100:5 vol./vol., 2-bromo-alpha-ergocryptine has an R_f -value of 0.40.

Pure 2-bromo-alpha-ergocryptine has a M.p. of 215°-217°C (decomp.), its specific rotation is $[\alpha]_D^{20} = -190^\circ$ to -192° (c=1, methylenechloride).

2-Bromo-alpha-ergocryptine in the form of the free base is insoluble and unsuitable for therapeutic use. Therefore, it is converted into a water-soluble, physiologically acceptable acid addition salt, preferably the salt of methanesulphonic acid.

The present invention provides a pharmaceutical or veterinary formulation which comprises such a salt formulated for pharmaceutical or veterinary use, respectively. The invention further includes a pharmaceutical or veterinary composition which comprises such a salt together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient. Such formulations and compositions may be in unit dosage form, e.g. capsules or tablets.

Also provided by the invention is a method for inhibiting the secretion of prolactin or growth hormone or for stimulating dopamine receptors in the CNS of an animal comprising the administration of an effective amount of such a salt, a formulation of the invention or a composition of the invention.

The present process is illustrated, but is not limited by the following Examples.

Example 1

2.3 g. (4.0 mmoles) of alpha-ergocryptine are dissolved in 100 ml. of pure dioxane at 20°C in a nitrogen atmosphere. With intensive stirring there is added a

solution of 2 g. (4.03 mmoles) of pyrrolidinone hydrotribromide and 0.12 g. (0.7 mmoles) of 2,2'-azo-bis-(2-methylpropionitrile) in 90 ml. of dioxane. After 30 minutes the reaction is interrupted and the solvent is evaporated *in vacuo*.

The dry residue is dissolved in 100 ml. of chloroform and extracted three times with 80 ml. portions of a 1% water solution of sodium carbonate. The chloroform phase is dried with sodium sulphate and evaporated to one seventh of the original volume. The concentrate is put on a column with a diameter of 5 cm., which is filled with 230 ml. of microporous glass CPG-75 wetted with chloroform. It is eluted with chloroform. The fractions containing 2-bromo-alpha-ergocryptine are combined and evaporated to dryness *in vacuo*. The dry residue is recrystallized from diisopropylether. 2.05 g. or 78.2% of theory of 2-bromo-alpha-ergocryptine are obtained with a M.p. of 215°-217°C and $[\alpha]_D^{20} = -190^\circ$ (c=1, methylenechloride).

Example 2

2.3 g. (4.0 mmoles) of alpha-ergocryptine are dissolved in 100 ml. of pure tetrahydrofuran in a nitrogen atmosphere.

With stirring there is added a solution of 1.08 g. (4.12 mmoles) of N-bromosaccharin and 0.13 g. (0.78 mmoles) of 2,2'-azo-bis-(2-methylpropionitrile) in 90 ml. of tetrahydrofuran. After completion of the reaction at room temperature, the solvent is evaporated *in vacuo*.

The dry residue is isolated and purified as described in Example 1.

2.1 g. or 80.1% of theory of 2-bromo-alpha-ergocryptine are obtained with a M.p. of 215°-218°C and $[\alpha]_D^{20} = -192^\circ$ (c=1, methylenechloride).

It should be clearly understood that we make no claim herein to a method for the prevention or treatment of disease in a human being.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. A process for the preparation of 2-bromo-alpha-ergocryptine, which process comprises brominating alpha-ergocryptine by the use of pyrrolidinone hydrotribromide or N-bromosaccharin in the presence of a free radical initiator.

2. A process as claimed in claim 1, wherein the bromination is effected in a cyclic ether solution under an inert atmosphere.

3. A process as claimed in claim 2, wherein the inert atmosphere comprises nitrogen.

4. A process as claimed in claim 2 or claim 3, wherein the cyclic ether is dioxane.

It is preferred that for each mole of alpha-ergocryptine 1 to 1.2 moles of brominating agent are used.

- 5 All starting substances mentioned are described in the literature and are normally available on the market.

- 10 2-Bromo-alpha-ergocryptine may be isolated from the reaction mixture by separation by chromatography using a column filled with microporous glass carrier, e.g. glass CPG-75 with 200-400 mesh and pore diameter of about 69Å a product of Electro Nucleonics, Fairfield, New Jersey, USA. Chloroform can be used as the eluting agent.

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- 20 2-Bromo-alpha-ergocryptine is a less polar compound than alpha-ergocryptine. On a silica gel plate Merck (registered Trade Mark) 60 upon development with mobile phase of chloroform/methanol 100:5 vol./vol., 2-bromo-alpha-ergocryptine has an R_f -value of 0.40.

- 25 Pure 2-bromo-alpha-ergocryptine has a M.p. of 215°-217°C (decomp.), its specific rotation is $[\alpha]_D^{20} = -190^\circ$ to -192° (c=1, methylenechloride).

- 30 2-Bromo-alpha-ergocryptine in the form of the free base is insoluble and unsuitable for therapeutic use. Therefore, it is converted into a water-soluble, physiologically acceptable acid addition salt, preferably the salt of methanesulphonic acid.

- 35 The present invention provides a pharmaceutical or veterinary formulation which comprises such a salt formulated for pharmaceutical or veterinary use, respectively. The invention further includes a pharmaceutical or veterinary composition which comprises such a salt together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient. Such formulations and compositions may be in unit dosage form, e.g. capsules or tablets.

- 50 Also provided by the invention is a method for inhibiting the secretion of prolactin or growth hormone or for stimulating dopamine receptors in the CNS of an animal comprising the administration of an effective amount of such a salt, a formulation of the invention or a composition of the invention.

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The dry residue is dissolved in 100 ml. of chloroform and extracted three times with 80 ml. portions of a 1% water solution of sodium carbonate. The chloroform phase is dried with sodium sulphate and evaporated to one seventh of the original volume. The concentrate is put on a column with a diameter of 5 cm., which is filled with 230 ml. of microporous glass CPG-75 wetted with chloroform. It is eluted with chloroform. The fractions containing 2-bromo-alpha-ergocryptine are combined and evaporated to dryness *in vacuo*. The dry residue is recrystallized from diisopropylether. 2.05 g. or 78.2% of theory of 2-bromo-alpha-ergocryptine are obtained with a M.p. of 215°-217°C and $[\alpha]_D^{20} = -190^\circ$ (c=1, methylenechloride).

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1. A process for the preparation of 2-bromo-alpha-ergocryptine, which process comprises brominating alpha-ergocryptine by the use of pyrrolidinone hydrotribromide or N-bromosaccharin in the presence of a free radical initiator.

2. A process as claimed in claim 1, wherein the bromination is effected in a cyclic ether solution under an inert atmosphere.

3. A process as claimed in claim 2, wherein the inert atmosphere comprises nitrogen.

4. A process as claimed in claim 2 or claim 3, wherein the cyclic ether is dioxane.



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5. A process as claimed in any one of claims 2 to 4, wherein the bromination is carried out at room temperature with stirring.

5 6. A process as claimed in any one of claims 1 to 5, wherein from 1 to 1.2 moles of the brominating agent are used per mole of alpha-ergocryptine.

10 7. A process as claimed in any one of claims 1 to 6, wherein said free radical initiator is 2,2'-azo-bis-(2-methylpropionitrile).

15 8. A process as claimed in any one of claims 1 to 7, wherein a microporous glass carrier separation column is used chromatographically to isolate the 2-bromo-alpha-ergocryptine from said reaction mixture.

20 9. A process as claimed in claim 1 and substantially as hereinbefore described in any one of the Examples.

25 10. A process as claimed in any one of claims 1 to 9 comprising the additional step of converting the 2-bromo-alpha-ergocryptine formed to a physiologically acceptable acid addition salt.

30 11. 2-bromo-alpha-ergocryptine which has been prepared by a process as claimed in any one of claims 1 to 9.

12. A physiologically acceptable acid addition salt of 2-bromo-alpha-ergocryptine which has been prepared by a process as claimed in claim 10.

13. A salt as claimed in claim 12, wherein the anion of the salt is methanesulphonate. 35

14. A pharmaceutical or veterinary formulation which comprises a salt as claimed in claim 12 or claim 13 formulated for pharmaceutical or veterinary use, respectively. 40

15. A pharmaceutical or veterinary composition which comprises a salt as claimed in claim 12 or claim 13 together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient. 45

16. A formulation as claimed in claim 14 or a composition as claimed in claim 15 in unit dosage form.

17. A method for inhibiting the secretion of prolactin or growth hormone or for stimulating dopamine receptors in the CNS of an animal comprising the administration of an effective amount of a salt as claimed in claim 12 or claim 13, a formulation as claimed in claim 14 or claim 16, or a composition as claimed in claim 15 or claim 16. 50 55

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