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3,752,888

2-BROMO- α -ERGOCRYPTINE AS A LACTATION INHIBITOR

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6 Claims

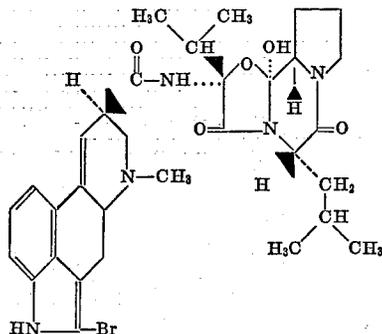
ABSTRACT OF THE DISCLOSURE

The invention concerns a novel method of inhibiting lactation in a warm-blooded female animal which comprises administering to the animal a dose of from about 0.03 milligram to about 10 milligrams per kilogram animal body weight of 2-bromo- α -ergocryptine.

A process for the production of 2-bromo- α -ergocryptine is also described.

This is a continuation in part of copending application Ser. No. 827,144 filed on May 23, 1969, now abandoned. The invention relates to a method of inhibiting lactation in a warm-blooded female animal.

In accordance with the invention, there is provided a method of inhibiting lactation in a warm-blooded female animal species, which comprises administering to the animal at intervals ranging from 4 times daily to once every ten days, a dose of from about 0.03 milligram to about 10 milligrams per kilogram animal body weight of 2-bromo- α -ergocryptine of the formula



or a pharmaceutically acceptable acid addition salt thereof.

An exemplary method employed for determining lactation inhibition, which shows the principle involved in such determinations, is as follows:

Each of a number of female rats having a body weight of 180–200 g. is placed in a tub together with a breeding male. About 18–19 days later, i.e. shortly before births take place, the pregnant female animals are individually placed in fresh tubs. Only 8 young animals of a litter were left with the mother animals. The litters were weighed to the nearest gram beginning from the morning of the first day after birth. The test substance was injected subcutaneously to the lactating mother animal on the evening of the 6th, 7th or 8th day after birth. The next day the broods were weighed in the morning and in the evening and on the following days only in the morning. Young animals from control broods, the mother animals of which were treated with solvent only, show an average weight increase from the day of the injection to the morning of the following day. The

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weight difference provides the standard for determining lactation inhibition. The average weight increase of the young animals from the morning of the injection day to the first weighing the following morning as compared to the standard is defined as the lactation inhibition.

Different animal species exhibit different sensitivity to treatment with 2-bromo- α -ergocryptine, and hence the dosage required to obtain satisfactory inhibition of lactation varies over a fairly wide range. Thus, for example, 2-bromo- α -ergocryptine is only moderately active in inhibiting lactation in the rat at a dose as high as about 4 mg./kg. animal body weight. In the rabbit on the other hand, a lactation inhibiting effect is observed at a subcutaneous dose of about 0.5 mg./kg. animal body weight [method employed by Cowie, A. T.: J. Endocr. 44, 437 (1969)]. A single subcutaneous dose of about 1 mg./kg. in the rabbit shows a lactation inhibiting effect of about 70% which lasts for about four days. After this period, milk yield regains the pretreatment level. Subcutaneous doses of 2 and 10 mg./kg. show inhibition of milk yield to about the same extent, but at these doses no recovery is observed within nine days. Observations in a mini-pig (of a weight of about 59 kg.) showed that three intramuscular doses of 0.1 mg./kg. in one day was followed by a phase of inhibited growth of the litter, which evidenced temporary inhibition of milk production. Observations with regular pigs (of weights ranging from 150 to about 180 kg.) showed that weight gain of the litters is inhibited in a significant dose-dependent fashion at intramuscular doses between 0.03 and 0.81 mg./kg. The mg./kg. dose at which satisfactory results are obtained in larger mammals of weight greater than about 2 kg. is seen from about 0.03 mg./kg. to about 1.0 mg./kg. conveniently given in divided doses two to three times a day or in sustained release form. For the larger mammals, the total practical daily dosage is in the range of from about 3 to about 15 mg. given in divided doses 2 or 3 times a day or in sustained release form. Convenient unit dosage forms suitable for oral administration contain from about 1 mg. to about 5 mg. of the compound, in association with pharmaceutical carriers or diluents. The dosage administered will, of course, vary depending upon the mode of administration and the extent of inhibition desired.

The methane sulphonate is a convenient pharmaceutically acceptable acid addition salt form of 2-bromo- α -ergocryptine. Capsules or tablets containing the unit dose of 2-bromo- α -ergocryptine in association with starches, sugars, talcum and the like are dosage forms suitable for oral administration. Injectable solutions, for example for administration by infusion, contain the 2-bromo- α -ergocryptine in association with conventional sterile diluents.

2-bromo- α -ergocryptine may be obtained by brominating ergocryptine in an inert solvent, with a mild brominating agent, e.g. N-bromophthalimide, N-bromosuccinimide or N-bromocaprolactam, and purifying the resulting 2-bromo- α -ergocryptine.

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 mol Br₂). Bromination is conveniently effected in an inert, polar solvent, e.g. dioxane, acetonitrile, or methylene chloride, at a temperature of 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 in-