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2,711,409

SALTS OF 8-HALOTHEOPHYLLINE AND ALKALI METAL SALTS OF AMINO ACIDS

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1 Claim. (Cl. 260—253)

This invention relates to a therapeutic product, and more particularly to a halo-theophylline-alkali metal salt of an aliphatic mono-amino carboxylic acid.

In the Krantz and Holbert Patent No. 2,433,765, dated December 30, 1947, there is described a pharmaceutical composition comprising an alkali salt of theophylline and an aliphatic amino acid. The composition of that patent is characterized by greatly increased solubility in water as compared with theophylline itself. While the composition of the patent referred to has diuretic properties, we have found that the therapeutic product of our present invention is much superior as a diuretic and has great usefulness in a particular field in which the composition of the patent has no practical value from a remedial standpoint.

We have now found that by the substitution of an 8-halo-theophylline for theophylline itself, a reaction product of 8-halo-theophylline, an aliphatic mono-amino carboxylic acid and an alkali metal hydroxide can be formed that has a marked therapeutic effect in the relief of premenstrual tension. A large percentage of women, estimated at from 30% to 60%, suffer from pre-menstrual tension in varying degrees during their menstrual age. These women accumulate water in the tissues during the week preceding the menses in varying amounts, usually from 1 to 5 pounds. Symptoms are headache, breast fullness and soreness, abdominal distension, low back pain, extreme nervousness, swelling of the ankles, increased appetite, irritability, pelvic pain and a feeling of tension. These symptoms are directly commensurate to the amount of fluid accumulated, or pounds of weight gained. Patients gaining up to two pounds during the week preceding the menses probably do not seek medical relief, but those that gain above two pounds become more conscious of the symptoms and usually do seek relief. Patients gaining from three and one-half to four pounds are almost incapacitated due to the severity of the symptoms from water toxemia. The product of our present invention is most outstanding in the relief of these symptoms. Patients to which our product is given approximately one week before onset of menses rarely gain more than one and one-half pounds, and in many cases there is no weight gained whatsoever. Furthermore, patients who are placed on treatment with our product, even after they have gained weight, have a diuresis within a few hours after beginning treatment, with resultant prompt relief of symptoms. The outstanding feature of our therapeutic product in the treatment of pre-menstrual tension is that in most patients it prevents water accumulation without diuresis if the treatment is started early enough so that the patients have no symptom of water toxemia through their premenstrual period.

It is, therefore, an important object of this invention to provide a product having enhanced therapeutic properties in the relief of pre-menstrual tension without, however, causing the patient to become nervous or jittery as is so often the case when theophylline compounds are used.

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It is a further important object of this invention to provide a therapeutic product capable of effectively unlocking pitressin induced edema in human females.

Other and further important objects of this invention will become apparent from the following description and appended claim.

The therapeutic product of our invention is prepared by reacting an 8-halo-theophylline, such as 8-bromo-theophylline or 8-chloro-theophylline, with an aliphatic mono-amino carboxylic acid in water solution in the presence of the proper amount of an alkali metal hydroxide, such as sodium or potassium hydroxide, or their equivalent. The aliphatic mono-amino carboxylic acids that are suitable for use in the preparation of our product include glycine, alpha-alanine, beta-alanine and glutamic acid. Equi-molal proportions of the 8-halo-theophylline and of the aliphatic amino carboxylic acid compounds are used, and an amount of alkali sufficient to neutralize the free carboxylic acid groups present, either as sodium hydroxide or some other alkali metal compound selected from the group consisting of sodium and potassium hydroxides, oxides and basic carbonates.

The following examples will serve to illustrate the method of preparing the various therapeutic products of our invention:

EXAMPLE 1.—BROMO - THEOPHYLLINE SODIUM GLYCINATE

One mole (259 g.) of bromo-theophylline was added to about one liter of water containing one mole (40 g.) of sodium hydroxide. One mole (75 g.) of glycine (amino-acetic acid) was added slowly, with stirring and slight warming, sufficient to effect complete solution. The slightly yellow solution was filtered, and the filtrate evaporated to dryness at reduced pressure and temperature. The solid material was ground to a white powder, giving almost quantitative yields. The physical properties of this product and of the products given in the following examples will be found summarized in Table I.

EXAMPLE 2.—CHLORO-THEOPHYLLINE SODIUM GLYCINATE

Chloro-theophylline and sodium hydroxide was prepared by the same procedure as given in Example 1, except that 0.1 mole (21.5 g.) of the chloro-theophylline was substituted for 0.1 mole (25.9 g.) of bromo-theophylline

EXAMPLE 3.—BROMO-THEOPHYLLINE POTASSIUM GLYCINATE

The reaction product of bromo-theophylline, glycine and potassium hydroxide was prepared by the same procedure as Example 1, except that 0.1 mole (5.6 g.) of potassium hydroxide was substituted for 0.1 mole (4.0 g.) of sodium hydroxide.

EXAMPLE 4.—BROMO-THEOPHYLLINE SODIUM ALANINATE (ALPHA AMINOPROPIONATE)

To 0.1 mole (4.0 g.) of sodium hydroxide in 150 cc. of water was added 0.1 mole (8.9 g.) of alpha-dl-alanine and 0.1 mole (25.9 g.) of bromo-theophylline. The resulting clear solution was evaporated to dryness at 60° C. and under reduced pressure to produce a white crystalline material.

EXAMPLE 5.—CHLORO-THEOPHYLLINE SODIUM ALANINATE

The procedure was the same as in Example 4, except that 0.1 mole (21.5 g.) of chloro-theophylline was substituted for 0.1 mole (25.9 g.) of bromo-theophylline.

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may be effected without departing from the scope of the novel concepts of the present invention.

We claim as our invention:

A therapeutic product consisting essentially of the salt of an 8-halo-theophylline in which the halo substituent is selected from the group consisting of bromine and chlorine, and an alkali metal salt of an aliphatic amino carboxylic acid selected from the group consisting of alanine, glycine and glutamic acid, the 8-halo-theophylline and alkali metal salt of the selected aliphatic amino carboxylic acid being in mole-to-mole ratio.

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References Cited in the file of this patent

UNITED STATES PATENTS

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