

1

3,541,209 METHOD OF ALLEVIATING HYPERTROPHIC CONDITIONS

Friedmund Neumann, Berlin, Germany,
assignor to Schering AG.

No Drawing. Continuation of application Ser. No.
536,311, Mar. 22, 1966. This application Oct. 12,
1967, Ser. No. 675,003

Claims priority, application Germany, Mar. 24, 1965,
Sch 36,759

Int. Cl. A61k 17/00

U.S. Cl. 424-243

7 Claims

ABSTRACT OF THE DISCLOSURE

This invention relates to a method for treating a patient suffering from hypertrophy of the prostate by intramuscular injection of 19-Nor-17 α -hydroxy-progesterone ester.

CROSS-REFERENCE

This application is a continuation of Ser. No. 536,311, filed Mar. 22, 1966, now abandoned.

The present invention relates to a method of alleviating certain hypertrophic conditions and to compositions therefor. More particularly, the present invention is concerned with the treatment of hypertrophic conditions of the prostate.

It is an object of the present invention to achieve with respect to the above described pathological conditions at least palliative relief, i.e., relief of pain, although frequently the present invention will cause a reduction in the size of the prostate and improvement of the urinary flow.

The essential active ingredient of the composition of the present invention is a 19-Nor-17 α -hydroxy-progesterone ester which, preferably, is administered by intramuscular injection in the form of an oily solution.

For instance, in the case of hypertrophy of the prostate which is characterized by its long duration, already within two or three months after starting of the treatment in accordance with the present invention a marked improvement is observed, particularly with respect to the irritating effects which occur in cases of hypertrophy of the prostate. Pollakisuria and nocturia are significantly reduced. Furthermore, the urine flow is normalized and the residual urine volume significantly reduced or completely eliminated.

Apart from the desired slow release or depot effect of, for instance, the 19-Nor-17 α -hydroxy-progesterone caproate, it is a particular advantage of the treatment according to the present invention that for successful treating of hypertrophy of the prostate a dosage of the effective active ingredient equal to between 100 and 200 mg. per week will give positive results. In contrast thereto, attempts to treat hypertrophy of the prostate with other steroid compounds generally require doses of between about 2 and 3 grams per week which are administered in the form of oily solutions. Even assuming a high solubility of the effective steroid of 250 mg. per 1 ml. oil, administration of these other steroids requires intramuscular injection of at least between 8 and 12 ml. oil which generally causes undesirable side effects such as oil infiltration, hardening at the point of injection, painful reddening and inflammation or even the formation of abscesses at the points of infiltration.

It is therefore an object of the present invention to provide a composition for, and a method of, treating patients suffering from the above described hypertrophy of the prostate, which method will result at least in an allevia-

2

tion of symptoms and frequently also in an objective improvement of the condition involved, and which can be carried out without causing severe side effects.

Other objects and advantages of the present invention will become apparent from a further reading of the description and of the appended claims.

With the above and other objects in view, the present invention contemplates a method of treating a patient suffering from hypertrophy of the prostate, which comprises administering to the patient by intramuscular injection an effective amount of a composition having as the essential active ingredient a 19-Nor-17 α -hydroxy-progesterone ester.

It is also within the scope of the present invention to provide an injectable liquid composition for intramuscular injection in the treatment of hypertrophy of the prostate, comprising a 19-Nor-17 α -hydroxy-progesterone ester and a pharmaceutical diluent.

Preferably, the 19-Nor-17 α -hydroxy-progesterone ester will be the formate, acetate, butyrate, caprylate, cyclopentylpropionate or caproate of 19-Nor-17 α -hydroxy-progesterone. Most preferably, the 19-Nor-17 α -hydroxy-progesterone caproate will be the essential active ingredient of the composition which is applied by intramuscular injection in accordance with the present invention.

Referring once more to the treatment of the hypertrophy of the prostate in accordance with the present invention, it is a further advantage that the esters which are utilized according to the present invention do not have an estrogenic or androgenic side effect and only a slight antigonadotropic effect.

Between 50 and 1000 mg. of the respective 19-Nor-17 α -hydroxy-progesterone ester are injected intramuscularly several times per week, and the preferred treatment will be the administration of 250 mg. between 2 and 3 times per week for the purpose of relieving pain, reduction of the size of prostate and improvement of urinary flow. The administration of this medication should be continued as long as the condition of the patient requires.

The composition which is to be administered in accordance with the present invention is formed by dissolving the 19-Nor-17 α -hydroxy-progesterone ester in oils such as castor oil by the methods conventionally employed in galenic pharmacy. If desired, the solubility of the oily solutions can be improved by the introduction of diluents or agents which will improve the solubility, for instance benzyl benzoate.

The solutions which are thus formed and which may contain, for instance, 250 mg. of the active agent per milliliter are then filled under sterile conditions into ampoules holding between 1 and 2 milliliters. A preferred composition according to the present invention is a solution of 19-Nor-17 α -hydroxy-progesterone-17 caproate in a mixture of 6 parts by volume castor oil and 4 parts by volume benzyl benzoate, containing 100 mg. of the caproate per milliliter.

The 19-Nor-17 α -hydroxy-progesterone esters are formed by esterification of 19-Nor-17 α -hydroxy-progesterone by means of the desired organic carboxylic acid, in accordance with methods which are known per se, for instance by esterification of the 19-Nor-17 α -hydroxy-progesterone with caproic acid/caproic acid anhydride and saponification of the 3-enolester group formed as intermediary, with aqueous sodium hydroxide solution. The isolated 19-Nor-17 α -hydroxy-progesterone caproate, after recrystallization from isopropyl ether, has a melting point of between 123 and 124° C.

More specifically, the esters which are preferred according to the present invention may be produced as described in the following examples.

3

EXAMPLE I

300 mg. of 17 α -hydroxy-19-norprogesterone are dissolved in a mixture of 17 cc. of acetic anhydride and 42 cc. of 95% formic acid which has been standing for 6 hours at 0° C. 345 mg. of p-toluene sulfonic acid·1 H₂O are added under ice cooling and nitrogen atmosphere. The reaction mixture is allowed to stand for 16 hours at room temperature. The clear solution is poured into a mixture of pyridine in ice water and filtered under suction after 1 hour to obtain the crude 17 α -hydroxy-norprogesterone-formiate as a precipitate. The precipitate is dried and recrystallized from isopropyl ether. There is thus obtained a yield of 265 mg. of pure 17 α -hydroxy-19-norprogesterone-17-formiate melting at 198–199.5° C.

U.V. ϵ_{239} = 17,000

EXAMPLE II

380 mg. of p-toluene sulfonic acid·1 H₂O are added to a suspension of 316 mg. of 17 α -hydroxy-norprogesterone in 16 cc. of acetic anhydride. The esterification is completed after 4 hours at 37° C. The excess of acetic anhydride is decomposed with pyridine in ice water and the 3-enol-17-diester is extracted with ether. The ether extract is washed until neutral, dried over sodium sulfate and concentrated. The residue was dissolved in 35 cc. of methanol, reacted with 0.35 cc. of concentrated hydrochloric acid and heated under refluxing for 1 hour. The methanolic solution is diluted with water and extracted with ether. The ether extract is washed with water until neutral and dried over sodium sulfate and then concentrated. The substance is recrystallized from isopropyl ether for purification. There is thus obtained a yield of 250 mg. of pure 17 α -hydroxy-19-norprogesterone-17-acetate melting at 214–216° C.

U.V. ϵ_{239} = 17,000

EXAMPLE III

1.32 g. of p-toluene sulfonic acid·1 H₂O are added to a solution of 1.0 g. of 17 α -hydroxy-19-norprogesterone in 32 cc. of caproic acid anhydride under stirring and under a nitrogen atmosphere. After 3 hours at 37° C. the reaction is completed. The clear light-yellow solution is taken up in a mixture of 1.43 cc. of concentrated hydrochloric acid in 143 cc. of methanol and heated under refluxing and under nitrogen for 1 hour. The excess caproic acid is removed by steam distillation and the residue is extracted with ether. The ether extract is washed with water until neutral, dried over sodium sulfate and concentrated. The precipitated crude product is recrystallized from isopropyl ether.

The yield amounts to 1.1 g. of pure 17 α -hydroxy-19-norprogesterone-17-caproate having a melting point of 123–124° C.

U.V. ϵ_{239} = 17,540

EXAMPLE IV

0.66 g. of p-toluene sulfonic acid·1 H₂O are added to a suspension of 0.5 g. of 17 α -hydroxy-norprogesterone in 20 cc. of butyric acid anhydride under stirring and under a nitrogen atmosphere. After 4 hours at 37° C., 70 cc. of methanol and 0.7 cc. of concentrated hydrochloric acid are added to the clear solution and the same is cooked for 1 hour under refluxing and under a nitrogen atmosphere. The excess is extracted with ether, the ether extract is washed until neutral, dried over sodium sulfate and concentrated.

Recrystallization from isopropyl ether results in the pure 17 α -hydroxy-19-norprogesterone-17-butyrate.

U.V. ϵ_{239} = 17,200

4

EXAMPLE V

920 mg. of p-toluene sulfonic acid·1 H₂O are added to a suspension of 0.7 g. of 17 α -hydroxy-19-norprogesterone in 30 cc. of caprylic acid anhydride under a nitrogen atmosphere. After 3 hours of stirring at 37° C. the solution is diluted with 100 cc. of methanol and after the addition of 1 cc. of concentrated hydrochloric acid it is heated for 1 hour under refluxing. The excess of caprylic acid is removed by steam distillation. The residue is taken up in ether, the ether extract is washed until neutral, dried over sodium sulfate and concentrated.

The thus obtained oil is dissolved in isopropyl ether, purified with activated carbon and the thus obtained colorless solution is again concentrated to dryness. The obtained oily residue is found upon elemental analysis and upon tests under ultraviolet and infrared light to be pure 17 α -hydroxy-19-norprogesterone-17-caprylate.

U.V. ϵ_{239} = 17,100

EXAMPLE VI

1 g. of 17 α -hydroxy-19-norprogesterone is added to a mixture heated to a temperature of 80° C. of 4 cc. of cyclopentylpropionic acid and 1 cc. of trifluoroacetic acid anhydride. After 45 minutes of reaction at the same temperature the clear solution is added to water, the precipitated oil is taken up in ether, the ether extract is first washed with a saturated sodium carbonate solution and subsequently with water until neutral. It is then dried over sodium sulfate and concentrated. The obtained crude oil is dissolved in isopropyl ether, purified with activated carbon, and the now obtained colorless solution is concentrated to dryness. A colorless oily residue can definitely be identified as 17 α -hydroxy-19-norprogesterone-17-cyclopentylpropionate.

U.V. ϵ_{239} = 17,400

The injectable liquid composition of the present invention may be prepared for instance of 25 mg. of 19-Nor-17 α -hydroxy-progesterone caproate by dissolving the same in 0.6 ml. of castor oil and 0.4 ml. of benzylbenzoate, or by dissolving the above caproate or other ester of 19-Nor-17 α -hydroxy-progesterone in 1.0 ml. of sesame oil.

Generally, it is desirable to use for intramuscular administration for the treatment of hypertrophy of the prostate, oily solutions containing between 50 and 250 mg. of the 19-Nor-17 α -hydroxy-progesterone ester per milliliter.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can by applying current knowledge readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention.

What is claimed as new and desired to be secured by Letters Patent is:

1. A method of treating a patient suffering from hypertrophy of the prostate, which comprises administering to said patient by intramuscular injection an effective amount of a composition including as the essential active ingredient a compound selected from the group consisting of the formate, acetate, butyrate, caprylate, cyclopentylpropionate and caproate of 19-Nor-17 α -hydroxy-progesterone.

2. A method as defined in claim 1, wherein said effective amount of said composition is such as to contain between about 50 and 1000 mg. of said 19-Nor-17 α -hydroxy-progesterone ester.

3. A method as defined in claim 1, wherein said effective amount of said composition is such as to contain about 250 mg. of said 19-Nor-17 α -hydroxy-progesterone ester.

5

4. A method as defined in claim 1, wherein intramuscular injection of said composition is carried out between 1 and 7 times per week.

5. A method as defined in claim 1, wherein said effective amount of said composition is such as to contain about 250 mg. of 19-Nor-17alpha-hydroxy-progesterone caproate; and wherein intramuscular injection of said composition is carried out between 2 and 3 times per week.

6. A method as defined in claim 1, wherein said essential active ingredient is 19-Nor-17alpha-hydroxy-progesterone caproate.

7. A method as defined in claim 1, wherein said effective amount of said composition is such as to contain between 100 and 1000 mg. of said 19-Nor-17alpha-hydroxy-progesterone caproate.

6

References Cited

FOREIGN PATENTS

876,902	9/1961	Great Britain.
1,074,582	2/1960	Germany.

OTHER REFERENCES

Varga: "Cancer Chemotherapy Abstracts," Medical Literature, Inc., May 22, 1962, vol. 3, No. 1, p. 48 (No. 273).

N.N.D., New and Nonofficial Drugs, J. B. Lippincott Company, 1964, pp. 661 and 662.

ALBERT T. MEYERS, Primary Examiner

J. D. GOLDBERG, Assistant Examiner