United States Patent [19]

Tyner

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[54] **17β-HYDROXY-16,16-DIMETHYLESTER-4-EN-3-ONE**

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[52] **U.S. Cl.**..... **260/397.4,** 260/397.5, 424/243

[51] **Int. Cl.**..... **C07c 169/22**

[56] **References Cited**

UNITED STATES PATENTS

3,049,555 8/1962 Tyner..... 260/397.4

3,280,156 10/1966 Tyner..... 260/397.4

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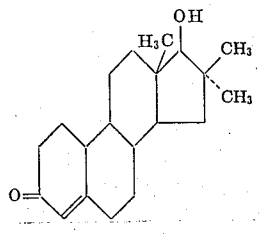
[57] **ABSTRACT**

Preparation of 17β-hydroxy-16,16-dimethylestr-4-en-3-one and its unexpected antiandrogenic and antisebum activities are disclosed.

1 Claim, No Drawings

17β-HYDROXY-16,16-DIMETHYLESTER-4-EN-3-ONE

This invention relates to a new, useful, and unobvious steroid having the chemical formula



and further characterized by antiandrogenic activity and the capacity to suppress the secretion of sebum.

The antiandrogenic activity of the steroid of this invention is remarkable because the corresponding 16-monomethyl steroid, a compound prepared by the instant inventor a number of years ago as disclosed in Example 7 of U.S. Pat. No. 3,049,555, has the opposite biological effect: it is androgenic. The monomethyl steroid also promotes anabolism, a possibly complicating side-effect which the dimethyl steroid of this invention does not share. Likewise androgenic and anabolic is another steroid which, were it not for unexpected difference in activity, might be considered closely-related, viz., 17′β-hydroxyspiro[cyclopropane- 1,16-estrk-4-en]-3′-one, a compound patented by the instant inventor in U.S. Pat. No. 3,280,156 and described in Example 9 thereof.

Tabulated immediately below are the results of standardized tests (according to U.S. Pat. No. 3,652,606 except that Badger rather than Sprague-Dawley rats were used) for anabolic and androgenic activity showing the unexpected absence of such activity which distinguishes 17β-hydroxy-16,16-dimethylestr-4-en-3-one. In the table, 17β-hydroxy-16,16-dimethylestr-4-en-3-one is designated "dimethyl," "monomethyl" refers to 17β-hydroxy-16β-methylestr-4-en-3-one, and "cyclopropyl" refers to 17′β-hydroxyspiro[cyclopropane-1,16′-estr-4-en]-3′-one. Each steroid was administered intramuscularly.

Compound	Total Dose (mg.)	Mean Wt. (mg.) Seminal Vesicles	Ventral Prostate	Levator Ani
dimethyl	5.0	8.0	9.8	68.5
control	0	7.3	7.6	60.5
monomethyl	5.0	23.1*	15.9*	116.5*
do.	1.0	8.8*	10.2**	73.5**
control	0	7.0	8.9	55.9
monomethyl	2.0	9.4*	11.4*	89.7*
do.	0.5	9.4*	9.8	72.4**
control	0	7.4	9.1	55.1
monomethyl	0.5	7.5	9.0	82.6*
do.	0.2	7.6	9.7	75.7
do.	0.1	7.7	9.7	83.3**
control	0	8.4	10.3	70.4
cyclopropyl	5.0	23.6*	17.0*	129.0*
control	0	7.1	9.2	61.1
cyclopropyl	1.0	10.9*	11.2*	88.2*
control	0	7.5	9.2	52.9
cyclopropyl	0.5	9.3*	10.3	88.7*
do.	0.2	9.1*	11.4	69.2*
do.	0.1	7.8	10.0	60.4
control	0	7.6	9.3	56.2

*statistically greater than concurrent controls at the 1% level of probability (P 0.01)

**statistically greater than concurrent controls at the 5% level of probability (P 0.05)

The antiandrogenic utility of 17β-hydroxy-16,16-dimethylestr-4-en-3-one is evident from the results of a test for its capacity to inhibit the testosterone-stimulated growth of seminal vesicle and prostate glands in castrated immature male rats. The procedure is as follows: 20 male Charles River rats are castrated at 22 days of age and separated into 2 equal groups such that for each animal in each group there is a littermate in the other. When the rats are about 36 days old, an implant consisting of a mixture of 8 mg. of testosterone, 8 mg. of Carbowax (polyethylene glycol), and 16 mg. of Flexo Wax C Light (non-crystalline hydrocarbon wax melting at 60°–64° C.) is inserted under the skin of each rat dorsally in the neck region. Beginning on the day of implant, the compound to be tested — dissolved or suspended in sesame oil, corn oil, or other physiologically inert vehicle — is administered subcutaneously to each animal in one group at a dose of 10 mg. per kg. daily for 24 successive days. The quantity of vehicle is such that a 180-gm. rat receives approximately 0.1 ml. at the beginning of the test and — with increasing body weight — approximately 0.2 ml. at the end. Each animal in the second group receives concurrent subcutaneous daily injections of vehicle likewise adjusted to body weight, and these animals serve as controls. On the day after treatment is concluded, the animals are sacrificed; and the seminal vesicle and ventral prostate glands are excised and dissected free of extraneous tissue. Fluid is expressed from the vesicles (but not the prostates), whereupon the glands are blotted and weighed. A compound is considered antiandrogenic if the mean weight of the vesicles in the group of animals treated therewith is significantly ($P \leqq 0.01$) less than the corresponding weight in the control group and there is a proportionate decrease in the mean prostate weight for treats vis-a-vis controls. 17β-Hydroxy-16,16-dimethylestr-4-en-3-one was active in this test.

The antisebum utility of 17β-hydroxy-16,16-dimethylestr-4-en-3-one is evident from the results of a standardized test for its capacity to decrease the amount of hair fat in rats, carried out essentially as described by F. J. Ebling in Proc. roy. Soc. Med., 62, 890 (1969). 1-7β-Hydroxy-16,16-dimethylestr-4-en-3-one was active subcutaneously at the 5 mg. per kg. dose level in this test.

Those skilled in the art will recognize that observations of activity in standardized tests for particular biological effects are fundamental to the development of valuable new drugs, both veterinary and human.

The preparation of 17β-hydroxy-16,16-dimethylestr-4-en-3-one can be accomplished as followed in three steps:

STEP I

3-Methoxy-16,16-dimethylestra-1,3,5(10)-trien-17β-ol

A solution of 377 parts of 3-methoxy-16,16-dimethylestra-1,3,5(10)-trien-17-one and 30 parts of sodium tetrahydroborate(1-) in 12,000 parts of 2-propanol is heated at the boiling point under reflux overnight. The resultant solution is cooled, acidified with a slight excess of acetic acid, concentrated to approximately 1/10 volume by vacuum distillation, and thereupon diluted with sufficient water to effect precipitation. After chilling, the precipitate is filtered off, washed with water, dried in air, and then recrystallized from a mixture of dichloromethane and ethyl acetate.

The product thus isolated is 3-methoxy-16,16-dimethylestra-1,3,5(10)-trien-17β-ol melting at 130°–133° C. and further characterized by a specific rotation — at 27° in 1.09 chloroform solution — of +72.5° (referred to the D line of sodium).

STEP II

3-Methoxy-16,16-dimethylestra-2,5(10)-dien-17β-ol

A solution of 314 parts of 3-methoxy-16,16-dimethylestra-1,3,5(10)-trien-17β-ol in 4,500 parts of tetrahydrofuran is added to a stirred solution of 4,000 parts of tert-butyl alcohol in 105,000 parts of redistilled liquid ammonia. Sufficient sodium metal is introduced portionwise with continued stirring to maintain a deep blue color for 2 hours, whereupon the ammonia is distilled off and the residual mixture steam distilled. From the chilled distillate, the granular solid is filtered out, washed with water, and dried at 60° C. in vacuo. The product thus isolated is 3-methoxy-16,16-dimethylestra-2,5(10)-dien-17β-ol melting in the range 140°–147° C.

STEP III

17β-Hydroxy-16,16-dimethylestr-4-en-3-one

To a stirred suspension of 10 parts of 3-methoxy-16,16-dimethylestra-2,5(10)-dien-17β-ol in 80 parts of methanol at room temperature under a nitrogen atmosphere is added approximately 5 parts of 18 percent hydrochloric acid. Approximately 1 ½ hours later, the resultant solution is diluted with 200 parts of water, and the mixture thus obtained is chilled. Insoluble solids are filtered out, washed with water, dried in air, and recrystallized from a mixture of methanol and ethyl acetate to give 17β-hydroxy-16,16-dimethylestr-4-en-3-one melting at 172°–175° C.

The steroid of this invention can be administered in dosage unit form including, but not necessarily limited to, sterile solutions or suspensions for intramuscular injection, intravaginal or rectal compositions such as suppositories, lozenges for sublingual administration, and salves or lotions (including sprayable solutions or mixtures) for topical application.

As is well-known in the pharmacological art, the appropriate dose in any given instance depends upon the nature of the condition treated and its severity, the route of administration, the species of mammal involved and its size and individual idiosyncrasies, etc. In general, and insofar as consistent with such factors, daily parenteral dosages of from 1 to about 5 mg. per kg. of body weight are suggested.

EXAMPLE 1

Preparation of sterile solution

A sterile solution containing 10 mg. per ml. of 17β-hydroxy-16,16-dimethylestr-4-en-3-one is prepared by dissolving 10 gm. thereof in 50 ml. of benzyl alcohol, diluting to 1 l. with polyethylene glycol 400, and then filtering to remove microorganisms.

EXAMPLE 2

Preparation of sterile suspension

A sterile suspension is prepared by mixing 100 gm. of sorbitol with 30 mg. of polyethylene glycol 400 and 4 mg. of benzyl alcohol, whereupon sterilization is effected by filtration and to the filtrate is added 250 mg. of sterile micronized 17β-hydroxy-16,16-dimethylestr-4-en-3-one. The resultant mixture is pulverized and smoothed in a sterile mill.

EXAMPLE 3

Preparation of suppositories

Suppositories are prepared to contain, individually, 250 mg. of 17β-hydroxy-16,16-dimethylestr-4-en-3-one by molding a mixture of 250 gm. of the micronized steroid, 800 gm. of polyethylene glycol 6,000, 600 gm. of polyethylene glycol 1,540, and 250 gm. of water into 1,000 suppositories.

EXAMPLE 4

Preparation of lozenges.

Lozenges are prepared to contain, individually, 60 mg. of 17β-hydroxy-16,16-dimethylestr-4-en-3-one by compressing a mixture of 60 gm. of the micronized steroid, 75 gm. of powdered polyethylene glycol 4,000, 75 gm. of powdered polyethylene glycol 6,000, and 150 gm. of mannitol into 1,000 lozenges.

EXAMPLE 5

Preparation of a salve

A mixture of 15 parts of stearyl alcohol, 4 parts of cetyl alcohol, and 20 parts of polyethylene glycol 400 is melted, whereupon 10 parts of 17β-hydroxy-16,16-dimethylestr-4-en-3-one is added with stirring. The resultant mixture is heated to 70°–75° C. and then added to 50 parts of water containing 1 part of sodium lauryl sulfate at the same temperature. The mixture thus obtained is stirred until it begins to cool and solidify.

Other vehicles which can be combined with 17β-hydroxy-16,16-dimethylestr-4-en-3-one to prepare a composition adapted to topical application comprise fatty alcohols, fatty acids, liquid petrolatum, glycerol monostearate, glycerol, propylene glycol and other polyalcohols, ethylene glycol polymers, surfactants, vegetable oils, fats, esters of fatty acids and fatty alcohols, water, and hydrous or anhydrous emulsion bases or gels.

What is claimed is:

1. 17β-Hydroxy-16,16-dimethylestr-4-en-3-one.

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