

1

3,354,185

1,2 METHYLENE ANDROSTANE DERIVATIVES

Rudolf Wiechert, Hans Mueller, and Friedmund Neumann, Berlin, Germany, assignors to Schering Aktiengesellschaft, Berlin, Germany

No Drawing, Filed Apr. 16, 1965, Ser. No. 448,854

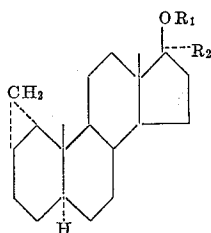
Claims priority, application Germany,

Apr. 25, 1964, Sch 35,037

6 Claims. (Cl. 260—397.5)

ABSTRACT OF THE DISCLOSURE

A steroid compound having the general structural formula

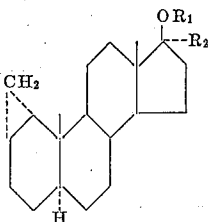


wherein R₁ is a member selected from the group consisting of hydrogen and acyl, acyl being derived from an aliphatic carboxylic acid having from 1 to 4 carbon atoms, and R₂ is a member selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl containing from 1 to 4 carbon atoms.

An example of the steroids is 1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol.

The compound has a strong anabolic and ovulation inhibiting action.

The invention relates to 1,2 α -methylene-5 α -androstane derivatives of the general formula



wherein R₁ is a member selected from the group consisting of hydrogen and acyl, acyl being derived from an aliphatic carboxylic acid having from 1 to 11 carbon atoms and R₂ is a member selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl containing from 1 to 4 carbon atoms.

It is an object of the present invention to improve the anabolic efficiency of steroids, particularly in case of oral application.

Another object of the invention is to improve the ovulation inhibitory activity of androstane type steroids.

A more specific object of the invention is the provision of a methylene substituted androstane type steroid with marked anabolic and ovulation inhibiting action.

These and other objects, as will be apparent from the following description of the invention, are accomplished by the compounds of the general formula above stated. The acyl group that may be present as R₁ in this formula may consist of any of the acid residues that are commonly used in steroid chemistry. Preferred acyl groups are the acid residues of aliphatic carboxylic acids and particularly those having 1 to 11 carbon atoms. Examples of such acids

2

are acetic acid, propionic acid, caproic acid, enanthic acid and undecylic acid. These acid residues can of course also be substituted in the usual manner. As examples in this respect are mentioned phenyl acetic acid, cyclopentylpropionic acid, halogenoacetic acid, amino-acetic acid, hydroxypropionic acid, etc.

The R₂ groups in the above stated formula may particularly be those having between 1 and 4 carbon atoms such as methyl, ethyl, ethinyl or vinyl.

The following Table 1 shows the strong oral anabolic action of the new compounds in item IV, relating to the 1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol. The oral anabolic and androgenic activity of the orally administered compound was determined by comparison with the corresponding activity of 17 α -methyltestosterone (item I), and of the well known anabolic agents II and III. The tests were carried out by standard methods using castrated rats and the Levator-ani and semicle vesicle test.

TABLE 1

No.	Substance 12 x 3 mg. P.O.	Levator-ani Weight, mg./100 g. rat	Semicle Vesicle Weight, mg./100 g. rat
I.....	17 α -methyl-testosterone.....	25	49
II.....	4-hydroxy-17 α -methyl-testosterone..	40	88
III.....	17 α -methyl-pyrazolo-[3,2-c]-5 α -androstane-17 β -ol.	26	28
IV.....	1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol.	43	59

Table 1 clearly demonstrates the superiority of the new compounds in respect of their anabolic efficiency. The extremely high dissociation between anabolic and androgenic action is illustrated by the subsequent Table 2.

TABLE 2

No.	Substance	Dose P.O., mg.	Levator-ani Weight, mg./100 g. rat	Semicle Vesicle Weight, mg./100 g. rat
I.....	17 α -methyl-testosterone	12 x 30	44	370
IV.....	1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol.	12 x 3	43	59

The 1,2 α -methylene-17 α -alkyl-5 α -androstane-17 β -ol compounds of the invention and their 17-esters, in addition to their anabolic action, are strong ovulation inhibitors. If we compare for instance the specific compound listed as IV with conventional ovulation inhibitors as shown below in Table 3 as items V to VIII we find a 10 to 30 times increased activity after oral application to normal female rats. The positive or negative ovulation in these tests was determined by tube inspection.

The following table lists the specific does (W_{D50}) which results in omission of ovulation in the case of 50% of the test animals and peroral administration.

TABLE 3

No.	Compound	W _{D50}	P.O. mg./animal/day (continued for four days)
V.....	17 α -ethinyl-19-nor-testosterone.....	3	-----
VI.....	17 α -ethinyl-19-nor-testosterone-acetate.	3	-----
VII.....	17 α -ethinyl- Δ^5 (10)-estrene-17 β -ol-3-one.	1-10	-----
VIII.....	6-chlor- Δ^5 -17 α -hydroxyprogesterone-acetate.	1-3	-----
IV.....	1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol.	0.1	-----

3

The new 1,2 α -methylene-5 α -androstane derivatives may be combined for therapeutical use with the additives, vehicles, taste modifiers, etc. common in galenic pharmacy and may be prepared in the form of tablets, lozenges, capsules, pills or also as suspensions or solutions. The selection of the concentration of active ingredient in drugs of this type depends of course on the indication for which it is intended. Oral anabolic agents for instance should contain about 1 to 20 mg. and ovulation inhibitors should contain about 0.5 to 5 mg. active substance.

Regarding the process of manufacture, the novel 1,2 α -methylene-5 α -androstane derivatives may for instance be made in the following manner. 1,2 α -methylene-5 α -androstane-17-one may be subjected to reaction with a Grignard agent in conventional manner in order to introduce an alkyl or alkenyl group in the place of the 17 keto group. In a similar manner can an alkynyl group be introduced, for instance the ethynyl group, which can then be reduced to the corresponding vinyl group or to a saturated alkyl group. Depending on what type of R₁ is desired in the final compound there may additionally be an esterification of the primarily formed steroid alcohols with the desired acid or a reactive derivative of such acid. The term "desired acid" should be understood as implying all acids conventionally used in steroid chemistry for the purpose of esterification of steroid alcohols.

The starting product of this process the 1,2 α -methylene-5 α -androstane-17-one has not heretofore been described, as far as we are aware. This compound can for instance be made as follows from 1,2 α -methylene-5 α -androstane-17 β -ol-3-one-17-acetate using conventional methods.

5 g. of 1,2 α -methylene-5 α -androstane-17 β -ol-3-one-17-acetate [Ber. 93, 1710 (60)] are heated for 20 minutes to 130° with 370 ml. ethylene-glycol and 25 ml. hydrazinhydrate of an 80% concentration. After cooling and addition of a solution of 37 g. sodium hydroxide in 37 ml. water heating is effected for two hours to 190 to 200° C. upon slow distillation. The reaction mixture is then again cooled and poured into a slightly acidified sodium chloride solution. The precipitate that forms is filtered off and dissolved in ether. After washing until neutral and drying the ether solution is concentrated by evaporation in vacuo. The residue is subjected to chromatography over silicagel (having 5% water content) with methylene chloride/chloroform (in a ratio of 3 to 1) and is triturated with pentane. There are obtained 2.74 g. of 1,2 α -methylene-5 α -androstane-17 β -ol having a melting point between 111.5 and 112° C.

4.1 g. of this product are dissolved in 5 ml. acetone. 1.25 g. of chromium(VI)-oxide in 4.7 ml. 8 N-sulfuric acid are added to the solution upon stirring and external cooling in ice water. The solution is then poured into an aqueous sodium chloride solution and is extracted with methylene chloride. After neutral washing, drying and concentration by evaporation of the methylene chloride phase there are left 4.0 g. of 1,2 α -methylene-5 α -androstane-17-one in the form of an oil.

The following examples will illustrate the making of the compounds of the invention without being intended as any limitation of the scope of the invention.

Example 1

A Grignard solution was prepared from 4.49 g. magnesium filings in 50 ml. abs. ether and 11.6 ml. methyl-iodide in 32.4 ml. abs. ether. 4.0 g. 1,2 α -methylene-5 α -androstane-17-one in 140 ml. abs. benzene were then added by dropping to the Grignard solution and were stirred for 4 hours at room temperature in a nitrogen atmosphere. Concentrated aqueous ammonium chloride solution was then cautiously added to the reaction mixture upon cooling with ice. The product was finally slightly acidified with dilute hydrogen chloride and extracted with ether. After separation the ether phase was washed until neutral, dried and concentrated by evaporation. The residue was subjected to chromatography over silicagel

4

(containing 5% water) with methylene chloride. There were obtained 3.06 g. 1,2 α -methylene-17 α -methyl-5 α -androstane-17 β -ol, M.P. 52-54° C. [α]_D²⁸: -4.85° (chloroform). Near—IR: 1.63 and 2.21 μ (cyclopropane); IR: 2.93 μ (OH), 8.70/9.09/9.34 μ (C—OH).

Example 2

Acetylene was passed for 30 minutes upon cooling into 133 ml. abs. tetrahydrofuran, A Grignard solution was prepared from 9.26 g. magnesium filings in 114 ml. abs. tetrahydrofuran and 29 ml. ethylbromide in 114 ml. abs. tetrahydrofuran. The cooled Grignard solution was added to the above solution of tetrahydrofuran resulting in a temperature rise to 45° C. The introduction of acetylene was continued until the reaction temperature went down again. 4.8 g. of 1,2 α -methylene-5 α -androstane-17-one in 114 ml. abs. tetrahydrofuran were then drop-added while continuing the passing of acetylene through the mixture. The reaction product was thereafter heated and stirred for 21 hours in an oil bath of a temperature of 70° C. and a nitrogen atmosphere. After cooling to 5° C. concentrated aqueous ammonium chloride solution was slowly added until there was no more reaction.

The product was thereupon extracted with ether, the separated organic phase was washed neutral with water and after drying over sodium sulfate was concentrated by evaporation in vacuo to dryness. The residue was subjected to chromatography over silicagel. By elution with carbon tetrachloride/methylenechloride (in a ratio of 2 to 1) one obtained 2.65 g. of 1,2 α -methylene-17 α -ethynyl-5 α -androstane-17 β -ol; M.P. 84-86° C.

[α]_D²⁸: -34.1° (chloroform). Near—IR: 1.63 and 2.21 μ (cyclopropane); IR: 2.95 μ (OH), 3.06 μ (CH of C $\equiv$ CH), 4.77 μ (C $\equiv$ C), 9.55/9.65/9.86/9.93 μ (C—OH).

Example 3

312 mg. of the product of Example 2 were dissolved in 30 ml. thiophene-free benzene and were hydrogenated in the presence of 312 mg. Lindlar catalyst [Helv. 35, 446 (52)] until 1 m. mole of hydrogen was absorbed. The product was thereafter filtered off from the catalyst and the solution was concentrated to dryness in vacuo. There were thus obtained 300 mg. 1,2 α -methylene-17 α -vinyl-5 α -androstane-17 β -ol in the form of an oil. [α]_D²⁸: +5.95° (chloroform) IR: 2.91 μ (OH), 6.1 μ (C=C), 9.82/10.0/10.90 μ (C—OH and CH=CH₂).

Example 4

312 mg. of 1,2 α -methylene-17 α -ethynyl-5 α -androstane-17 β -ol were hydrogenated in 30 ml. thiophene-free benzene in the presence of 2 $\times$ 312 mg. Lindlar catalyst up to step-by-step absorption of 2 m. mole of hydrogen. The solution was then filtered off from the catalyst and was concentrated to dryness at 40° in vacuo. There were thus obtained 300 mg. of 1,2 α -methylene-17 α -ethyl-5 α -androstane-17 β -ol in the form of an oil. [α]_D²⁸: +0.95° (chloroform). IR: 2.87 μ (OH), 9.87/10.27 μ (C—OH).

Example 5

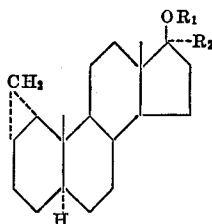
A mixture of 500 mg. 1,2 α -methylene-17 α -ethynyl-5 α -androstane-17 β -ol, 2.5 ml. pyridine and 2.5 ml. acetic acid anhydride were heated for 4 hours to 130-140° C. The reaction mixture was then stirred into an iced sodium chloride solution and was extracted with ether. After neutral washing, drying and concentration by evaporation of the separated ether solution there were obtained 425 mg. 1,2 α -methylene-17 α -ethynyl-5 α -androstane-17 β -ol-17-acetate in the form of an oil.

All of these examples are intended for illustration only, as has previously been noted, and we therefore do not wish to be limited otherwise than by the language of the appended claims.

5

We claim:

1. A compound having the general structural formula



wherein R_1 is a member selected from the group consisting of hydrogen and acyl, acyl being derived from an aliphatic carboxylic acid having from 1 to 11 carbon atoms, and R_2 is a member selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl containing from 1 to 4 carbon atoms.

2. 1,2 α -methylene-17 α -methyl-5 α -androstande-17 β -ol.3. 1,2 α -methylene-17 α -ethynyl-5 α -androstande-17 β -ol.

6

4. 1,2 α -methylene-17 α -vinyl-5 α -androstande-17 β -ol.5. 1,2 α -methylene-17 α -ethyl-5 α -androstande-17 β -ol.6. 1,2 α - methylene - 17 α - ethynyl - 5 α - androstande-17 β -ol-17-acetate.

5

References Cited

UNITED STATES PATENTS

3,163,663	12/1964	Cross et al.	260—397.5
3,242,050	3/1966	Wiechert	260—397.5
3,254,099	5/1966	Jolles et al.	260—397.5

10

OTHER REFERENCES

Fieser et al.: "Steroids," Reinhold Publishing Corp.,
New York, N.Y., 1959, pages 492, 493, 621, 627 and 630.

LEWIS GOTTS, *Primary Examiner.*J. R. BROWN, *Assistant Examiner.*

20