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NOVEL 17-ETHERS OF 19-NORTESTOSTERONE

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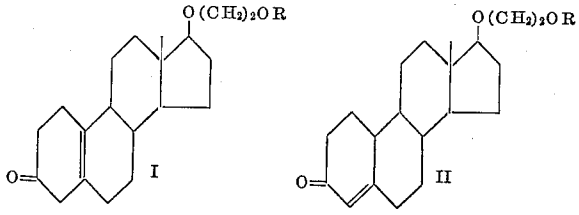
5 Claims. (Cl. 260—397.4)

This invention relates in general to novel compositions of matter classified in the art of chemistry as steroids and methods for manufacturing and using such compositions.

The invention which applicants desire to patent in its chief product aspect is particularly concerned with the concept and physical embodiment of a series of novel 17-ethers of 19-nortestosterone and its functional equivalents such as the corresponding 17-ethers of its 5(10)-3-one analogs. Typically compounds which fall within the metes and bounds of applicants' invention are those having the general Formulae I and II:



wherein the symbol R represents either hydrogen or a lower alkyl group such as methyl, ethyl, or propyl, for example, which are preferred, but which may also include other lower alkyl groups containing up to about 7 carbon atoms such as isopropyl, butyl, isobutyl and the like radicals.

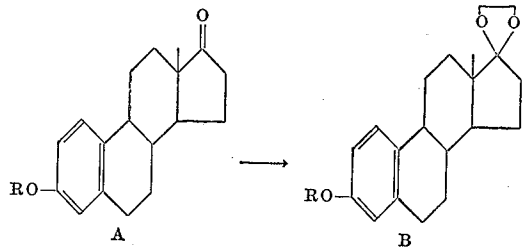
The compounds of the present invention in their tangible embodiment form as well as their graphic representation as shown above, are considered useful steroidal anabolic agents which have particular efficacy because of their low androgenic activity in concert with a favorable anabolic activity. Moreover the tangible embodimnets of the compositions represented by Formula II are also active progestational agents. In particular those compounds wherein R represents hydrogen have demonstrated a satisfactory level of progestational activity when evaluated in test animals. In addition to the aforesaid uses, some of the compounds of both series are hormones, specifically exhibiting anti-inflammatory activity as well as being useful for their general hormonal properties.

As employed herein, the term "lower alkyl radicals" is intended to refer to those alkyl groups which include both straight and branch chain alkyl radicals, among which are the alkyl radicals specifically noted above as well as the cycloalkyl lower alkyl radicals, cyclohexyl and cyclopentyl, which would be expected to perform in a like manner.

Our preferred manner of making and using our invention will be generally described so as to enable one versed in the art of chemistry to make and use the embodiments thereof as follows:

(a) *Preparation of starting materials.*—As generally and particularly described and claimed in our copending application Ser. No. 310,485 filed Sept. 20, 1963, a typical starting material for the preparation of the compounds of this invention such as the typical starting material 17β-(2-hydroxyethoxy)-3-methoxyestra-1,3,5(10)-triene may be prepared by hydrogenolysis of the corresponding 17,17-ethylene ketal analogs with a suitable reducing agent, but preferably with one such as lithium aluminum hydride aluminum chloride, as more particularly detailed therein.

In this preparation the nature of the 17-ether group of the end product obtained can be controlled by the selection of a suitable 17,17-alkylene ketal starting material. In the instant case, illustratively, the 17,17-ethylene ketal would be the compound, 3-methoxy-17,17-ethylenedioxyestra-1,3,5(10)-triene. Moreover, if it is desired to obtain final products wherein the ether group in position 17 is an alkyloxyalkyl radical, the 17-hydroxyalkyl ethers obtained in the first step may be further reacted with a suitable alkylating agent such as diazomethane and the like by the use of conventional alkylation technique as more particularly described in our aforesaid copending application, Ser. No. 310,485. The 17-ketals of 1,3,5(10)-estratrienes from which the 17-ethers of 1,3,5(10)-estratrienes are prepared are themselves manufactured as disclosed in H. Smith et al. copending application Ser. No. 219,135, filed Aug. 24, 1962, now Patent No. 3,138,588. In the Smith application, the 17,17-substituted alkylenedioxy type analogs are prepared from the corresponding 17-ketones by treatment under conventional ketalizing conditions. A typical general reaction would be the following:

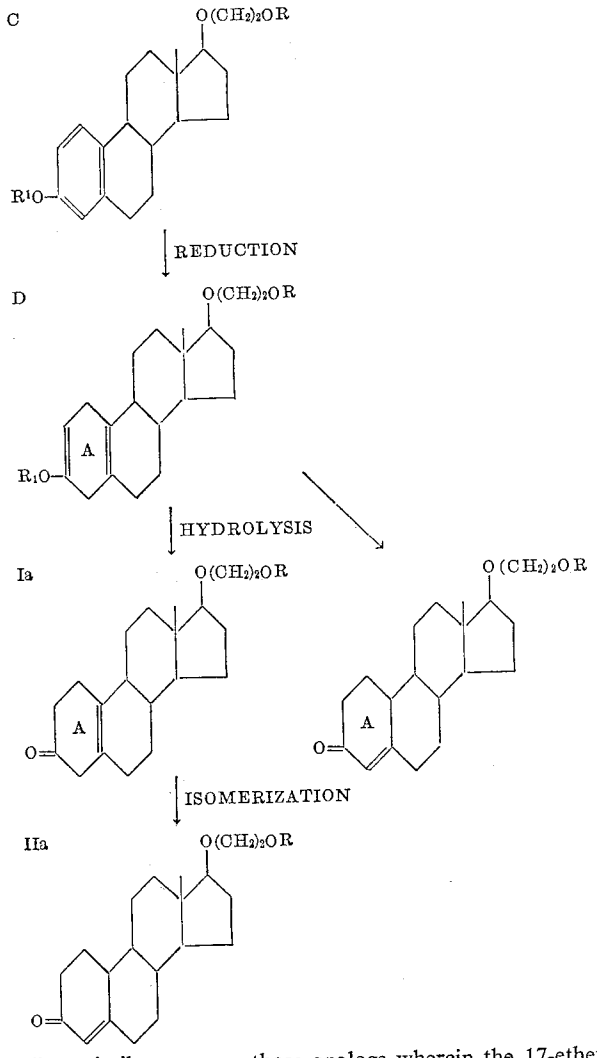


In the above reaction, the 17-ketone (A), wherein R may be lower alkyl, cycloalkyl and the like is transformed to the 17-ketal (B), as noted in Ser. No. 219,135 in greater detail.

As indicated above generally and more particularly in S.N. 310,485 filed Sept. 20, 1963, a steroidal 17-ketal of S.N. 219,135 illustrated by compounds of structure (B) above is reduced to the 17-ether alcohol, which affords the starting compounds for this particular invention. The 17-position substituted 1,3,5(10)-estratriene compounds of S.N. 219,135 and S.N. 310,485 are not included as the subject matter of this invention and are noted herein for completeness of disclosure, since these separately inventive materials are separately disclosed and claimed in the aforesaid copending applications referred to above.

(b) *Preparation of final products.*—In our preferred mode of synthesis the starting materials of the type illustrated in our S.N. 310,485 such as the typical starting compound 17β-(2-hydroxyethoxy)-3-methoxyestra - 1,3,5(10)-triene (C), is selectively A-ring reduced with a suitable reducing agent, preferably lithium and 1-methoxy-2-propanol, in a suitable organic reaction solvent such as liquid ammonia with constant agitation (as in Example 1 below). It may be noted that in addition to the reaction solvent employed, cosolvents such as tetrahydrofuran may be used (as stated in Example 2 below). The crude enol ether product obtained from the reduction step is designated as product (D) in the following flow sheet. When (D) is treated with a weak acid such as oxalic acid, the ether group in position 3 is transformed into a keto group to produce compound (Ia) 17β-(2-hydroxy ethoxy)estr-5(10)-en-3-one. A compound of type (IIa), which has a 4(5) double bond rather than a 5(10) double bond, may be obtained by treatment of (Ia) with a suitable strong acid/methanol solution to shift the double bond. Alternately, (IIa), may be directly obtained by acid hydrolysis of (D) with a strong acid.

These reactions may be generally represented:



In a similar manner, those analogs wherein the 17-ether group is of the alkyloxyalkyl type may be obtained by selection of a suitably substituted (C) type starting material, with R representing an alkyl group.

In the above reaction sequence, the symbol R represents either hydrogen or a lower alkyl group. The symbol R', where it appears, represents a lower alkyl group.

In an alternate method of preparation as specifically illustrated in Example 4 below, the 4(5)-A-ring unsaturated compounds can be obtained directly by hydrolysis of a 2,5(10)-diene such as the compound 17-(2-hydroxyethoxy)-3-methoxyestra-2,5(10)-diene by treatment with a strong acid such as hydrochloric acid to obtain a compound such as 17β-(2-hydroxyethoxy)estr-4-en-3-one.

These and other like variants of our inventive concept will undoubtedly occur to those skilled in the art and are intended to be included within the metes and bounds of our inventive concept.

The following several examples will illustrate the preferred mode of operation of our invention. However, they are purely intended for purpose of illustration, and may not be construed to limit the concept involved in any manner. For a legal definition of the scope of the invention, attention may be directed only to the several appended claims.

Example 1.—d-17β-(2-hydroxyethoxy)estr-5(10)-en-3-one

Treat a mixture of 2.9 g. of d-17β-(2-hydroxyethoxy)-3-methoxyestra-1,3,5(10)-triene, 100 ml. of 1-methoxy-2-propanol and 300 ml. of liquid ammonia with 3.0 g. of lithium during 30 minutes while stirring. After adding 6.0 g. of ammonium chloride and water, filter off the enol ether and dry in vacuo to yield 2.1 g.; I.R. 3.0; 5.9; 6.0μ; U.V. essentially no aromatic.

Add a 700 mg. sample of the enol ether to a solution of 1.0 g. of oxalic acid dihydrate, 10 ml. of water, and 50 ml. of methanol, and stir for 2 hours under nitrogen. Dilute the reaction mixture with water and extract with ether. Recrystallize the residue obtained after evaporation of the solvent from ethylacetate-hexane to yield 300 mg. of d-17β-(2-hydroxyethoxy)estr-5(10)-en-3-one; M.P. 84–88°.

Found: C, 75.72; H, 9.48. $C_{20}H_{30}O_3$: C, 75.43; H, 9.50.

Example 2.—d-17β-(2-methoxyethoxy)estr-5(10)-en-3-one

Treat a mixture of 2.5 g. of d-17β-(2-methoxyethoxy)-3-methoxyestra-1,3,5(10)-triene, 75 ml. of 1-methoxy-2-propanol, 75 ml. of tetrahydrofuran and 300 ml. of ammonia with 2.5 g. of lithium during 30 minutes. After adding 20 ml. of absolute alcohol followed by 2.5 g. of ammonium chloride, precipitate the product with water to yield 1.5 g. of the enol ether; I.R. 5.6; 6.0μ; U.V. essentially no aromatic.

Add the enol ether to a solution of 2.0 g. of oxalic acid dihydrate in 20 ml. of water and 100 ml. of methanol, and stir the reaction mixture under nitrogen for 2 hours. After adding water, extract the product with ether. Wash the organic layer with a saturated sodium bicarbonate solution, followed by brine, and finally dry over magnesium sulfate. On evaporation of the ether, 17β-(2-methoxyethoxy)estr-5(10)-en-3-one can be obtained. I.R. 5.75μ.

Example 3.—d-17β-(2-ethoxyethoxy)estr-5(10)-en-3-one

Substitute d-17β-(2-methoxyethoxy)-3-methoxyestra-1,3,5(10)-triene with d-3-butoxy-17β-(2-ethoxyethoxy)estra-1,3,5(10)-triene, and carry out the reaction as described for Example 2, d-17β-(2-ethoxyethoxy estr-5(10)-en-3-one is obtained.

Example 4.—d-17β-(2-hydroxyethoxy)estr-4-en-3-one

Add a 2.1 g. sample of d-17β-(2-hydroxyethoxy)-3-methoxyestra-2,5(10)-diene to a solution of 110 ml. of methanol, 8 ml. of concentrated hydrochloric acid, and 5 ml. of water. Stire for 30 minutes, dilute the resulting clear solution with water and extract with ether. Wash the organic layer with saturated sodium bicarbonate solution and brine, and finally dry over magnesium sulfate. After evaporation of the solvent, recrystallize the crude product from acetone-petroleum ether to yield 1.1 g. of d-17β-(2-hydroxyethoxy)estr-4-en-3-one; M.P. 113–114°; I.R. 2.90; 6.00; 6.18μ; U.V. 241 mμ (ε 15,600).

Found: C, 75.15; H, 9.48. $C_{20}H_{30}O_3$ requires: C, 75.43; H, 9.50%.

Example 5.—d-17β-(2-hydroxyethoxy)estr-4-en-3-one

When treating d-17β-(2-hydroxyethoxy)estr-5(10)-en-3-one with a solution methanol, hydrochloric acid, and water, using the method outlined in Example 7, d-17β-(2-hydroxyethoxy)estr-4-en-3-one can be obtained.

Example 6.—d-17β-(2-methoxyethoxy)estr-4-en-3-one

When treating d-17β-(2-methoxyethoxy) - 3 - methoxyestra-2,5(10)-diene with a solution of methanol, hydrochloric acid, and water by applying the procedure outlined in Example 4, d-17β-(2-methoxyethoxy)estr - 4-en-3-one can be obtained.

Example 7.—d-17β-(2-methoxyethoxy)estr-4-en-3-one

Treat a 1.0 g. sample of d-17β-(2-methoxyethoxy)estr-5-(10)-en-3-one with a solution of 50 ml. of methanol, 5 ml. of hydrochloric acid and 4 ml. of water for 30 minutes. Dilute the reaction mixture with water and extract with ether. Recrystallize the residue obtained on evaporation of the ether from ethyl acetate-hexane to yield 350

mg. of the product; M.P. 73–75°; U.V. 241 mμ (ε 16,900); I.R. 5.96; 6.20μ.

Found: C, 75.92; H, 9.55. $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%.

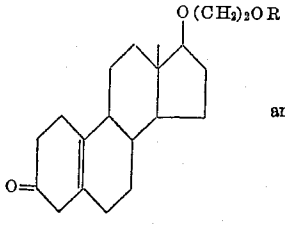
Example 8.—d-17β-(2-ethoxyethoxy)estr-4-en-3-one

Substitute d-17β-(2-methoxyethoxy) - 3 - methoxyestra-1,3,5(10)-triene with d-3-butoxy - 17β-(2-ethoxyethoxy) estra-1,3,5(10)-triene and carry out the reaction as outlined in the procedure of Example 2, the 1,4-dihydro compound can be obtained.

When treating this compound with a solution of methanol and aqueous hydrochloric acid using the procedure outlined in Example 4, d-17β-(2-ethoxyethoxy)estr-4-en-3-one can be obtained.

We claim:

1. A 17-ether of a steroid selected from the group consisting of those having one of the general structural formulae:



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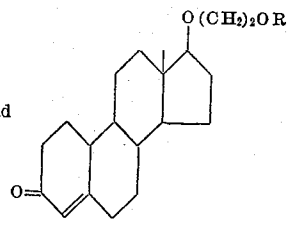
and



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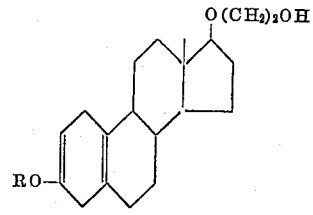
wherein R represents a substituent selected from the group consisting of hydrogen and lower alkyl.

2. 17β-(2-hydroxyethoxy)estr-5(10)-en-3-one.
3. 17β-(2-hydroxyethoxy)estr-4-en-3-one.
4. 17β-(2-methoxyethoxy)estr-4-en-3-one.
5. A compound of the formula:



wherein R is lower alkyl.

References Cited

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ELBERT L. ROBERTS, *Primary Examiner.*