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2-LOWER-ALKYL AND 2,17α-DI-LOWER-ALKYL DERIVATIVES OF TESTOSTERONE AND OF 19-NORTESTOSTERONE, AND INTERMEDIATES THEREFOR

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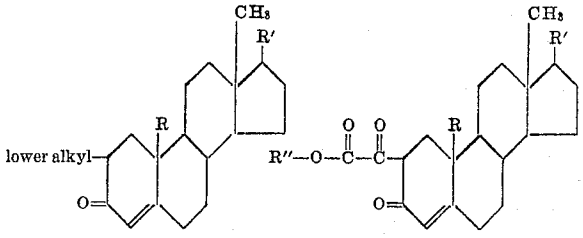
The present invention relates to novel steroid compounds and is more particularly concerned with 17-oxygenated 2-lower-alkyl-3-keto-4-androstene compounds and certain intermediate 2-glyoxylates and their alkali metal salts, particularly lower-alkyl [3-keto-17α-methyl-17β - hydroxy - 4 - androstene - 2 - yl] glyoxylate, lower-alkyl [3 - keto - 17β - hydroxy - 19 - nor - 4 - androstene-2-yl] glyoxylate, lower-alkyl [3,17-diketo-4-androstene-2-yl]glyoxylate; lower-alkyl [3,17-diketo-19-nor-4-androstene-2-yl] glyoxylate; lower-alkyl [3-keto-17α-methyl - 17β - hydroxy - 19 - nor - 4 - androstene - 2-yl] glyoxylate and the alkali metal salts thereof.

The novel compounds of the present invention may be represented by the following formulae:



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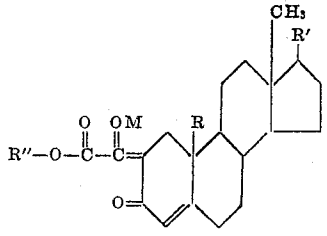
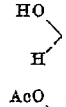


III

wherein lower-alkyl contains from one to eight carbon atoms; R is selected from the group consisting of hydrogen and methyl; R' is selected from the group consisting of



wherein the acyl group is of a hydrocarbon carboxylic acid containing from one to eight carbon atoms, inclusive,

and keto; wherein R'' is a lower-alkyl, defined as above; and wherein M is an alkali metal of atomic weight 6 through 40.

The process of the instant invention requires oxalylation of a 17-oxygenated-3-keto-Δ^4-androstene compound with a lower-alkyl oxalate, alkylation of the thus produced 17 - oxygenated - 2 - lower - alkyloxyoxalyl - 3-keto-Δ^4-androstene compound with a lower-alkyl halide, hydrolysis to remove the lower-alkoxyoxalyl group and chromic acid oxidation of the corresponding 2-alkyl-testosterone to produce 17-keto compounds. In addition, organic carboxylic acid esters, preferably hydrocarbon carboxylic acid esters wherein the acid contains from one to eight carbon atoms, inclusive, are produced from 2-methyltestosterones, obtained by the instant procedure, in conventional manner such as by esterifying the selected 2-methyltestosterone with an esterifying agent such as an acid, a hydrocarbon carboxylic acid chloride or bromide, ketene, ketenes of organic acids, isopropenyl acylates, or the like.

It is an object of the instant invention to provide physiologically active 17-oxygenated 2-lower-alkyl-3-keto-Δ^4-androstene compounds, 2-glyoxylates and the alkali metal salts thereof. A further object of the instant invention is the production of such 17-oxygenated 2-lower-alkyl-3-keto-Δ^4-androstene compounds and the intermediate 2-glyoxylates and alkali metal salts thereof. A particular object of the instant invention is to produce the 2-methyl derivatives of 17-oxygenated 3-keto-Δ^4-androstenes, such as 2-methyltestosterone, 2-methyl-19-nortestosterone, 2, 17α-dimethyltestosterone, the precursor glyoxylates thereof, and the sodium and potassium salts thereof. Other objects of the present invention will be apparent to those skilled in the art to which this invention pertains.

The instantly produced compounds are physiologically and pharmacologically active per se and are also useful intermediates for the preparation of other physiologically active compounds. 2-methyl-19-nortestosterone is a compound of significant anabolic activity possessing neither significant androgenic nor estrogenic activity such as found in 19-nortestosterone. 2-methyltestosterone and 2,17-dimethyltestosterone are also anabolically active, the latter being particularly active when given orally. Both of these have very low androgenic and estrogenic activity. The glyoxylates of these compounds are also anabolically active, with low androgenic and low estrogenic actvity. In addition, these compounds favorably influence the metabolism of minerals such as sodium, potassium or calcium.

The compounds of this invention possess anti-inflammatory and gonadotrophic function and are also useful as antifungal and antibacterial compounds.

An injectable composition of the present invention to promote protein anabolism, such as to be advantageous in the treatment of cachexias is as follows:

	Mg.
Sodium citrate, U.S.P.	5.7
Sodium carboxymethylcellulose, low viscosity	5.0
Plasdone (polyvinylpyrrolidone)	5.0
Polysorbate 80, U.S.P.	4.0
Sterile methylparaben, U.S.P. (methyl para-hydroxybenzoate)	1.5
Sterile propylparaben, U.S.P. (propyl para-hydroxybenzoate)	0.2
2-methyl-19-nortestosterone	50.0
Water for injection, q.s.-ad, 2.0 cc.	

The 2-methyltestosterones and 2-methyl-4-androstene-3,17-diones are useful as intermediates in the preparation of active compounds in the pregnane series, for example, by oxidation of the testosterones to the corresponding 2-methyl-4-androstene-3,17-diones which can be reacted with acetylene to produce the corresponding 2-methyl-17β-ethinyl testosterone.. Hydrogenation of the 2-methyl ethinyl testosterone with palladium in pyridine gives the corresponding 2-methyl-17-vinyl-testosterone,

which by allylic rearrangement and hydroxylation yields the corresponding 2-methyl-17α,20,21-trihydroxy-4-pregnene-3-one as was done by Reichstein, Helv. Chim. Acta 24, 945 (1941), and 22, 755 (1939), with 17-ethinyl testosterone. Oxidation of 2 - methyl - 17α,20,21 - trihydroxy-4-pregnene-3-one with manganese dioxide produces 2-methyl-17α,21-dihydroxy-4-pregnene-3,20-dione, the 2-methyl derivative of Reichstein's substance S. In the same manner, from the corresponding 2-methyl-19-nortestosterone and 2-methyl-19-nor-4-androstene-3,17-dione, the corresponding 2-methyl-19-nor compound S is obtained. Fermentation of the 2-methyl compound S with *Curvularia lunata* produces the corresponding 2-methyl - 11β,17α,21 - trihydroxy - 4 - pregnene - 3,20-dione, that is 2-methyl hydrocortisone, a compound known in the art as active.

The starting material of the instant invention are 17-oxygenated-3-keto-Δ^4-androstene compounds known in the art, such as 4-androstene-3,17-dione, testosterone, esters of testosterone, 19-nortestorterone, 17α-methyl-testosterone, 19-nor-4-androstene-3,17-dione, 17α-methyl-19-nortestosterone, or the like.

In carrying out the process of the instant invention the selected 17-oxygenated-4-androstene-3-one is glyoxylated, dissolved in an organic solvent such as benzene, toluene, xylene, and the like, aromatic hydrocarbons, methanol, ethanol, isopropyl alcohol, tertiary butyl alcohol, and other alcohols, etc., hydrofuran, dioxane, diethyl ether, Skellysolve B hexane hydrocarbon, and other aliphatic hydrocarbons, mixtures of these solvents and other essentially non-reactive solvents. Benzene, with or without small percentages of added alkanol, or tertiary butyl alcohol is the preferred solvent. The condensation is generally conducted at a temperature between about zero degree centigrade and the boiling point of the reaction mixture. Usually the reaction proceeds with satisfactory rapidity at between about room temperature and about 70 degrees centigrade, and temperatures substantially above or below this range are therefore not necessary. The time essential to obtain substantially complete reaction varies considerably, between about five minutes and several days, depending upon the reaction solvent, the reaction temperature, the selected ester of oxalic acid and the alkali metal condensation catalyst employed. When sodium methoxide and methyl or ethyl oxalate are employed at about fifty degrees centigrade, the reaction is usually more than half completed in a few minutes. The condensation step is generally carried out in the absence of any significant amount of water. To insure the essentially complete absence of water from the reaction mixture, the solvent is suitably carefully dried over a drying agent, such as, for example, anhydrous sodium sulfate, calcium sulfate, calcium chloride, phosphorus pentoxide, sodium or the like, or when an aromatic hydrocarbon is used as a solvent, a portion of the solvent is distilled before using. Alkali metal condensation catalysts include the alkali metal alkoxides, for example, sodium methoxide, sodium ethoxide, sodium isopropoxide, potassium tertiary butoxide, lithium methoxide, and the like, alkali metals, such as alkali metal hydrides, alkali metal amides and alkyl alkali metals, for example, sodium amide, triphenylmethyl sodium, and the like. Of these, the alkali metal alkoxides, especially sodium methoxide and sodium ethoxide are preferred for their convenience and consistently satisfactory results.

The theoretical proportion of alkali metal condensation catalysts required is one mole per mole of steroid. Somewhat more than the theoretical proportion is usually employed, however. The presence, of substantially greater than one molar equivalent of lower-alkyl oxalate per mole of starting steroid, is also advantageous and promotes rapid completion of the reaction. The reaction is therefore usually carried out in the presence of greater than about one molar equivalent of the selected ester. Esters, preferably of oxalic acid which are conveniently employed in the process of the present invention, include the lower-alkyl esters, for example, methyl, ethyl, propyl, butyl, isobutyl, amyl, hexyl, heptyl, and octyl esters of oxalic acid, and the like. Since methyl and ethyl oxalates appear to undergo condensation with the starting steroids, most rapidly these esters are preferred.

The thus produced alkali metal anolate may be separated by the addition of a large volume of an organic solvent in which the alkali metal enolate is insoluble, such as ether, pentane, hexane, or benzene, for example. Another method of purifying alkali metal enolate comprises acidification of a cold aqueous solution of the thus precipitated alkali metal enolate to precipitate the free enol and then treating a solution of the free enol in ether or benzene with a chemical equivalent of sodium methoxide thus reprecipitating the sodium enolate. When the condensation is carried out in the presence of substantial amounts of methyl or ethyl alcohol, the removal of said alcohol by distillation at reduced pressure before the addition of an additional amount of solvent is preferred if a high yield of isolated product is to be obtained.

The thus obtained alkali metal enolate of 2-lower-alkyloxy-oxalyl-3-keto-Δ^4-androstene represented by formula III, is alkylated with a lower-alkyl halide, wherein the halogen has an atomic weight from 78 to 131, inclusive, and wherein the lower-alkyl group contains from one to eight carbon atoms, inclusive, to produce a 2-lower-alkoxyoxalyl-2-lower-alkyl-3-keto-Δ^4-androstene. The usual reaction conditions and solvents employed in the alkylation of an active methylene compound are employed in the alkylation process. For example, a convenient method of alkylation involves the addition of the selected alkyl halide to the reaction product resulting from the condensation step, preferably after the decomposition of any excess alkali metal condensation catalyst.

The reaction is continued for several hours, for example, about eight to about 72 hours at a reaction temperature of about room temperature (twenty to thirty degrees centigrade). Higher reaction temperatures require lower reaction times.

Satisfactory yields are also obtained by stirring the solution of the free active methylene compound with the selected alkyl halide in the presence of the selected alkali metal alkylation catalyst. Such alkali metal alkylation catalyst comprises, for example, alkali metal alkoxides preferably containing from one to eight carbon atoms, illustratively sodium methoxide, sodium ethoxide, lithium methoxide, potassium tertiary butoxide, etc., alkali metals, alkala metal hydrides, alkali metal amides, triphenylmethyl sodium, sodium or potossium carbonate, or the like.

The thus produced 2-alkoxyoxalyl-2-alkyl-3-keo-Δ^4-androstene is usually not isolated but used for the next step, removal of the alkoxyoxalyl group. This reversal step, removal of the alkoxyoxalyl group, is produced by adding water to the basic solution and is further favored by the presence of hydroxide or alkoxide ions, particularly, methoxide and ethoxide ions. The reversal reaction is usually performed at room temperature between twenty to thirty degrees centigrade by allowing the alkaline mixture to stand for a period of one-half hour to 24 hours. At a temperature of 25 degrees centigrade, a period of one to four hours is sufficient to produce the reversal reaction. The thus obtained product, a 2-lower-alkyl-3-keto-Δ^4-androstene is isolated from the mixture by conventional methods such as extraction with water-immiscible solvents, for example, methylene chloride, dichloroethylene, chloroform, carbon tetrachloride, benzene, ether, or the like. Purification of the thus obtained product is obtained by standard procedures, such as recrystallization, chromatography, or the like, as deemed necessary.

If the thus produced 2-lower-alkyl-3-keto-Δ^4-androstene, possessed a hyrodlyzable acyloxy group, (e.g. 2-alkyltestosterones 17β-acylate), such acyloxy group may be

removed by hydrolysis during the reversal reaction. 2-alkyltestosterone 17-esters wherein the acyl group is of a simple unhindered hydrocarbon carboxylic acid, such as acetic, propionic, butyric, benzoic, or the like, are usually completely hydrolyzed, while 17-esters of hindered acids such as trimethylacetic, triethylacetic, 2,2-dimethylpropionic, dineopentylacetic acid, remain substantially intact during the reversal reaction. If the 17-acyloxy group is desired and has been removed during the reversal reaction, reesterification is effected by standard methods such as by reacting the 2-lower-alkyl-3-keto-Δ^4-androstene-17-ol in pyridine solution with an acid anhydride, acid halide, ketene, ketenes of long chain hydrocarbon carboxylic acid, or the like, at room temperature at about 25 degrees centigrade to produce the desired ester.

Oxidation of the 17-hydroxyl group of a 2-lower-alkyl-3-keto-Δ^4-androstene-17-ol produces the corresponding 2-lower-alkyl-4-androstene-3,17-dione. The oxidation is carried out in conventional manner, for example, by oxidation of the corresponding 2-lower-alkyl compound with chromic acid in acetic acid solution or in a heterogeneous system, such as stirring sodium or potassium dichromate, in acidified aqueous solution with a solution of the steroid in a water-immiscible solvent such as methylene dichloride, ethylene dichloride, using vigorous agitation to get the reactants in closer contact. The time to complete the oxidation depends mainly on the temperature and reactant concentration and thus varies between one-half hour to 48 hours, at room temperature between two to ten hours.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting.

Example 1

Methyl [3-keto-17β-hydroxy-4-estren-2-yl] glyoxylate

A solution containing 5.48 grams of 3-keto-Δ^4-estren-17β-ol (19-nortestosterone), 64 milliliters of tertiary butyl alcohol and 4.7 grams of methyl oxalate was prepared by warming to about 55 degrees centigrade. A solution containing 1.62 grams of sodium methoxide in 6.8 milliliters of methanol solution was added to the warm tertiary butyl alcohol solution above. The reaction mixture was maintained for fifteen minutes. Then 65 milliliters of ether was added, and the precipitated mixture was agitated for an additional period of fifteen minutes. The thus obtained slurry was filtered and washed with ether and dried to yield 6.0 grams of crude methyl [3-keto-17β-hydroxy-4-estren-2-yl] glyoxylate sodium salt. The salt was dissolved in 100 milliliters of water and cooled in an ice bath, dilute hydrochloric acid was added until the solution was acidic, at which time the steroid had separated as a solid. The reaction mixture was filtered, the thus collected precipitate washed with water and dried to yield 5.4 grams of methyl [3-keto-17β-hydroxy-4-estren-2-yl] glyoxylate of melting point 85 to 87 degrees centigrade,

$\lambda_{max.}^{alc.}$ 248, 326 mmu

In the same manner condensing 17α-methyl-19-nortestosterone with methyl oxalate and hyrolyzing with acid the thus obtained sodium salt of methyl [3-keto-17α-methyl-17β-hydroxy-19-nor-4-androstene-2-yl] glyoxylate yields the free methyl [3-keto-17α-methyl-17β-hydroxy-19-nor-4-androstene-2-yl] glyoxylate.

Example 2

Methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate

In the same manner as shown in Example 1, condensing eight grams of 17α-methyltestosterone with methyl oxalate in the presence of sodium methoxide to obtain the sodium enolate of methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate and hydrolyzing with dilute hydrochloric acids the sodium enolate of methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate yielded 6.82 grams of methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate of

$\lambda_{max.}^{alc.}$ (.01N H_2SO_4) 252 mu (7,025), 326 mu (5,675)

Treating the methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate thus obtained in ether solution with a chemical equivalent amount of sodium methoxide precipitates the sodium enolate of methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate.

Example 3

Methyl [3-keto-17β-hydroxy-4-androstene-2-yl] glyoxylate

In the same manner as given in Example 1, 11.53 grams of testosterone dissolved in tertiary butyl alcohol were treated with methyl oxalate in the presence of potassium methoxide to give the potassium salt of methyl [3-keto-17β-hydroxy-4- androstene-2-yl] glyoxylate which was hydrolyzed with dilute hydrochloric acid in water to give 9.90 grams of methyl [3-keto-17β-hydroxy-4-androstene-2-yl] glyoxylate of melting point 78 to 82 degrees centigrade,

$\lambda_{max.}^{acid\ alcohol}$ 254, 326

Analysis:—Calculated for $C_{22}H_{30}O_6$: C, 70.56; H, 8.08. Found: C, 69.94; H, 8.01.

Example 4

Ethyl [3,17-diketo-4-androstene-2-yl] glyoxylate

In the same manner as shown in Example 1, 4-androstene-3,17-dione was reacted with ethyl oxalate in the presence of lithium ethoxide to give the lithium salt of ethyl [3,17-diketo-4-androstene-2-yl] glyoxylate. Treating the lithium salt in water solution with dilute hydrochloric acid precipitates ethyl [3,17-diketo-4-androstene-2-yl] glyoxylate.

In the same manner as shown in Examples 1 through 4, other lower-alkyl [3-keto-17-oxygenated-4-androstene-2-yl] glyoxylates are produced by reacting the corresponding lower-alkyl oxalate such as methyl, ethyl, propyl, butyl, valeryl, hexyl, heptyl, and octyl oxalate in the presence of a sodium, potassium, or lithium methoxide or sodium, potassium, or lithium ethoxide to give the corresponding alkali-metal enol salt of lower-alkyl [3-keto-17-oxygenated-4-androstene-2-yl] glyoxylate which is decomposed with a dilute mineral acid to give the free lower-alkyl [3-keto-17-oxygenated-4-androstene-2-yl] glyoxylate. Representative lower-alkyl [3-keto-17-oxygenated-4-androstene-2-yl] glyoxylates thus obtained comprise: ethyl [3-keto-17β-hydroxy-4-androstene-2-yl] glyoxylate, ethyl [3-keto-17β-trimethylacetoxy-4-androstene-2-yl] glyoxylate, methyl [3-keto-17β-benzoyloxy-4-androstene-2-yl] glyoxylate, methyl [3,17-diketo-4-androstene-2-yl] glyoxylate, ethyl [3,17-diketo-19-nor-4-androstene-2-yl] glyoxylate, methyl [3,17-diketo-19-nor-4-androstene-2-yl] glyoxylate and methyl [3-keto-17β-benzoyloxy-19-nor-4-androstene-2-yl] glyoxylate.

Example 5

2-methyl-17β-4-estren-3-one-(2-methyl-19-nortestosterone)

A solution containing one gram of methyl [3-keto-17β-hydroxy-4-estren-2-yl] glyoxylate, ten milliliters of acetone, and three milliliters of methyl iodide was prepared. Anhydrous potassium carbonate (four grams) was added and the mixture was stirred for a period of 64 hours. Thereafter the reaction mixture was diluted with fifty milliliters of water and extracted with three thirty-milliliter portions of methylene chloride. Evaporation of the methylene chloride extracts gave 0.89 gram of residue which was dissolved in five milliliters of methanol and thereto was added 167 milligrams of sodium methoxide in 0.7 milliliter of methanol. The solution was allowed to stand at about 25 degrees centigrade for a period of two hours. Thereafter the reaction mixture was diluted

with thirty milliliters of water and extracted with three twenty-milliliter portions of methylene chloride. The combined extracts were then washed, dried, and concentrated to give 0.72 gram of residue containing the 2-methyl-3-keto-4-estren-17β-ol. The crude product was dissolved in 25 milliliters of methylene chloride, 25 milliliters of Skellysolve B hexanes were added and the mixture was chromatographed over 60 grams of Florisil anhydrous magnesium silicate. Fractions of 65 milliliters of eluant were taken as follows:

1–15	Skellysolve B-hexanes:acetone 95:5
16–18	Skellysolve B-hexanes:acetone 90:10
18–20	Skellysolve B-hexanes:acetone 80:20

Fractions 6 and 7 were combined and recrystallized from two milliliters of acetone and two milliliters of Skellysolve B hexanes to give 0.21 gram of crystalline, pure 2-methyl-19-nortestosterone (2-methyl-17β-hydroxy-4-estren-3-one), of melting point 169 to 180 degrees

$\lambda_{max.}^{alc.}$ 239.5 mmu

ϵ=14,700, rotation $[\alpha]_D$ plus 88 degrees (c. 0.586 in $CHCl_3$).

Analysis.—Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.01; H, 10.22.

Example 6

2,17α-dimethyl-17β-hydroxy-4-androstene-3-one (2,17-dimethyltestosterone)

In the same manner as shown in Example 5, methyl [3-keto-17α-methyl-17β - hydroxy - 4 - androstene - 2 - yl] glyoxylate was reacted with methyl iodide in the presence of anhydrous sodium carbonate The reaction mixture was diluted with water and extracted with chloroform and the chloroform evaporated. The thus remaining residue methyl [3-keto-2,17α-dimethyl-17β-hydroxy-4-androstene-2-yl] glyoxylate was decomposed in ethanol in the presence of sodium ethoxide to give pure 2,17α-dimethyl-17β-hyroxy-4-androstene-3-one of melting point 156 to 157 degrees centigrade, rotation $[\alpha]_D$ plus 91 degrees (alcohol).

Analysis.—Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 80.10; H, 10.49.

Example 7

2-methyl-17β-hydroxy-4-androstene-3-one (2-methyltestosterone)

In the same manner as shown in Example 5, treating five grams of methyl [3-keto-17β-hydroxy-4-androstene-2-yl] glyoxylate in acetone with methyl iodide in the presence of potassium carbonate gave 5.31 grams of a mixture containing methyl [2-methyl-3-keto-17β-hydroxy-4-androstene-2-yl] glyoxylate. Hydrolysis of this material with sodium methoxide in methanol and isolation gave a residue of 4.10 grams containing 2-methyltestosterone. This crude 2-methyltestosterone was dissolved in fifty milliliters of methylene chloride, fifty milliliters of Skellysolve B was added and the thus prepared solution was chromatographed over 260 grams of Florisil magnesium silicate using 500-milliliter fractions of solvent:

1–4	Skellysolve B:acetone 95:5
5–15	Skellysolve B:acetone 94:6
16–20	Skellysolve B:acetone 90:10

Fractions 8 through 13 were combined and recrystallized from acetone Skellysolve B to give 2-methyltestosterone of melting point 159 to 161 degrees, rotation $[\alpha]_D$ plus 123 degrees centigrade (c., 1.021 in chloroform).

Analysis.—Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.70; H, 9.95.

Example 8

2,17-dimethyl-17β-hydroxy-19-nor-4-androstene-3-one

In the same manner as given in Example 5, treating methyl [3-keto-17α-methyl-17β-hydroxy-19-nor-4-androstene-2-yl] glyoxylate with methyl iodide in acetone solution and hydrolyzing with sodium ethoxide in ethanol gave 2,17 - dimethyl-17β-hydroxy-19-nor-4-androstene-3-one.

Example 9

2-ethyl-17β-hydroxy-4-estrene-3-one

In the manner given in Example 5, methyl [3-keto-17β-hydroxy-4-estrene-2-yl] glyoxylate was treated with ethyl iodide in acetone solution to give methyl [2-ethyl-3-keto-17β-hydroxy-4-estrene - 2 - yl] glyoxylate which was hydrolyzed with sodium methoxide in methanol to yield 2-ethyl-17β-hydroxy-4-estrene-3-one.

Example 10

2-n-propyl-4-androstene-3,17-dione

In the same manner as shown in Example 5, methyl [3, 17-diketo-4-androstene-2-yl] glyoxylate was treated with normal propyl iodide in acetone solution to give methyl [2-n-propyl-3,17-diketo-4-androstene-2-yl] which was hydrolyzed with sodium hydroxide in ethanol to yield 2-n-propyl-4-androstene-3,17-dione.

Example 11

2-methyltestosterone-17-propionate

To a solution of 0.5 gram of 2-methyltestosterone in five milliliters of pyridine was added three milliliters of propionic anhydride. The solution was allowed to stand for 24 hours whereafter it was poured onto 50 milliliters of ice. The resulting mixture was then allowed to stand for another 24 hours in a refrigerator at five degrees centigrade and thereafter filtered. The precipitate collected was recrystallized from acetone and Skellysolve B hexanes to give pure 2-methyltestosterone-17-propionate.

Example 12

2-methyltestosterone benzoate

0.5 gram of 2-methyltestosterone, dissolved in five milliliters of pyridine was reacted as shown in Example 10, with three milliliters of benzoyl chloride. The mixture was maintained at room temperature for a period of 24 hours, thereafter poured into ice water and maintained another 24 hours in a refrigerator at a temperature between five and ten degrees centigrade. The mixture was thereafter filtered and the precipitated crude 2-methyltestosterone 17β-benzoate was recrystallized to give pure 2-methyltestosterone 17β-benzoate.

In the same manner as shown in Examples 11 and 12, other esters of 2-methyltestosterone benzoate are prepared by reacting 2-methyltestosterone with esterifying agents such as hydrocarbon carboxylic acid halides, especially chlorides and bromides or with hydrocarbon carboxylic acid anhydrides. Representative such 2-methyltestosterone 17β-acylate are the 2-methyltestosterone-17β-acetate, chloroacetate, bromoacetate, fluoroacetate, iodoacetate, trichloroacetate, butyrate, isobutyrate, valerate, isovalerate, hexanoate, heptanoate, octanoate, phenylacetate, phenylpropionate, anisate, succinate, salicylate, tartrate, citrate, acid maleate, toluenesulfonate, or the like.

Example 13

2-methyl-4-androstene-3,17-dione

A solution was prepared consisting of 0.5 gram of 2-methyltestosterone, 25 grams of glacial acetic acid, and one milliliter of water. To this solution was added 150 milligrams of chromic anhydride, the mixture was shaken and maintained at room temperature at 25 degrees centigrade for a period of 18 hours. Thereafter the mixture was poured into 100 milliliters of ice water, neutralized by the addition of sodium bicarbonate solution, refrigerated to about five to ten degrees centigrade for a period of eighteen hours and thereafter filtered to give 2-methyl-

4-androstene-3,17-dione which was recrystallized from acetone and Skellysolve B to give pure 2-methyl-4-androstene-3,17-dione.

EXAMPLE 14

2-methyl-19-nor-4-androstene-3,17-dione

In the same manner as given in Example 13, 2-methyl-19-nortestosterone was oxidized with chromic acid in acetic acid solution to give 2-methyl-19-nor-4-androstene-3,17-dione.

In the same manner as shown in Examples 5 through 10, treating lower-alkyl [3-keto-4-androstene-2-yl] glyoxylate with a lower-alkyl halide such as methyl iodide or bromide, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, phenyl or benzyl iodide or bromide, and thereafter hydrolyzing the resulting lower-alkyl [2-lower-alkyl-3-keto-4-androstene-2-yl] glyoxylate produces other 2-lower-alkyl-3-keto-4-androstenes such as, for example, 2-ethyl-17β-hydroxy - 4 - estrene-3-one, 2-benzyl-17β-hydroxy-4-estrene-3-one, 2-propyltestosterone, 2-isopropyltestosterone, 2-benzyltestosterone, 2-phenyltestosterone, 2-hexyltestosterone, 2-butyl - 17α - methyl-17β-hydroxy-4-androstene-3-one, 2-pentyl-17α-methyl - 17β - hydroxy-4-androstene-3-one, 2-hexyl - 17α - methyl-17β-hydroxy-4-androstene - 3 - one, 2-octyl-17α-methyl-17β-hydroxy-4-androstene-3-one, and 2-ethyl-17α-methyl-17β-hydroxy-4-androstene-3-one.

Oxidation of 2-alkyltestosterone and 2-alkyl-19-nortestosterone compounds with chromic acid in the manner shown in Examples 13 and 14 is productive of 2-alkyl-4-androstene-3,17-diones and 2-alkyl-19-norandrostene-3,17 - dione such as 2-ethyl-4-androstene-3,17-dione, 2-propyl-4-androstene - 3,17 - dione, 2 - hexyl-4-androstene-3,17-dione, 2-benzyl-4-androstene-3,17-dione, 2-ethyl-19-nor-4-androstene-3,17-dione, 2-propyl - 19 - nor-4-androsstene-3,17-dione, 2-heptyl-4-androstene-3,17-dione, and the like.

Esterification of 2-alkyltestosterones and 2-alkyl-17β-hydroxy-4-estrene-3-ones with organic acid anhydrides or halides, preferably anhydrides or halides of hydrocarbon carboxylic acid containing from one to eight carbon atoms, inclusive, in the manner shown in Examples 11 and 12, is productive of the corresponding esters of such 2-alkyltestosterones and 2-alkyl-19-testosterones such as, for example, 2-ethyl-17β-acetoxy-4-estrene-3-one, 2-benzyl-17β-propionyloxy-4-estrene-3-one, 2 - propyltestosterone propionate, 2-isopropyltestosterone benzoate, 2-benzyltestosterone acetate, 2 - phenyltestosterone phenylacetate, 2-hexyltestosterone valerate, and the like.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. 2-methyl-19-nortestosterone.

2. 2-methyl-17β-hydroxy-4-androstene-3-one.

3. 2,17α-dimethyl-17β-hydroxy-4-androstene-3-one.

4. The sodium enolate of methyl [3-keto-17α-methyl-17β-hydroxy-4-androstene-2-yl] glyoxylate.

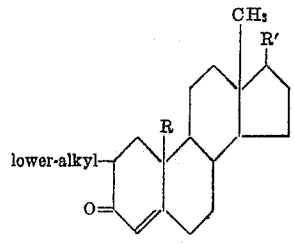
5. Ethyl [3,17-diketo-4-androstene-2-yl] glyoxylate.

6. 2-glyoxylates and their alkali metal salts selected from the group consisting of lower-alkyl [3-keto-17β-hydroxy - 19 - nor-4-androstene-2-yl] glyoxylate; lower-alkyl [3,17-diketo-4-androstene-2-yl] glyoxylate; lower-alkyl [3,17-diketo-19-nor-4-androstene-2-yl] glyoxylate; and the alkali metal salts thereof, wherein lower-alkyl contains from one to eight carbon atoms, inclusive, and the alkali metal is of atomic weight six through forty.

7. 2-glyoxylates and their alkali metal salts selected from the group consisting of lower-alkyl [3-keto-17α-methyl-17β-hydroxy - 4 - androstene-2-yl] glyoxylate and lower-alkyl [3-keto-17α-methyl-17β-hydroxy - 19 - nor-4-androstene-2-yl] glyoxylate; and the alkali metal salts thereof, wherein lower alkyl contains from one to eight carbon atoms, inclusive, and the alkali metal is of atomic weight six through forty.

8. 2,17α-dimethyl-19-nortestosterone.

9. A compound selected from the group consisting of 17-oxygenated-4-androsten-3-one of the formula:

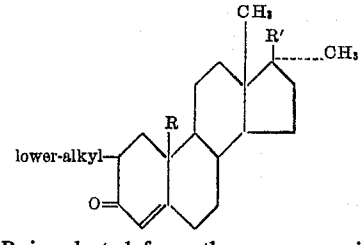


wherein the 2-lower-alkyl group contains from one to eight carbon atoms, inclusive, R is selected from the group consisting of hydrogen and methyl, R' is selected from the group consisting of keto

and

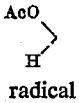
in which Ac is an acyl radical of a hydrocarbon carboxylic acid containing from one to eight carbon atoms, inclusive.

10. A 2-lower-alkyl-17α-methyl-4-androsten-3-one of the formula:



wherein R is selected from the group consisting of hydrogen and methyl, R' is selected from the group consisting of

and



in which Ac is the acyl radical of a hydrocarbon carboxylic acid containing from one to eight carbon atoms, inclusive.

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