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6,1'-SPIROCYCLOPROPYL COMPOUNDS OF THE ANDROSTANE SERIES

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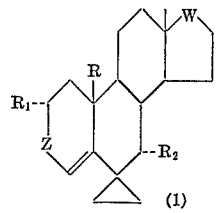
U.S. Cl. 260—397.4 17 Claims

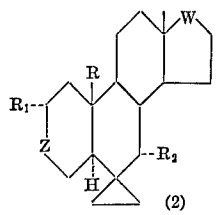
ABSTRACT OF THE DISCLOSURE

Compounds of the class of 6,1'-spirocyclopropyl androstanes and androstenes useful as anabolic, androgenic, estrogenic, hypocholesteremic, antifertility and progestational agents and processes for their production.

This invention relates to novel 6,1'-spirocyclopropyl compounds of the androstane series, to processes for the production thereof and to novel intermediates. More particularly, this invention relates to compounds represented by the following structural formulae:



(1)



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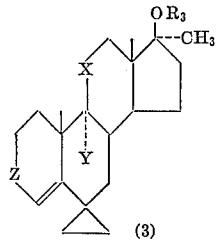

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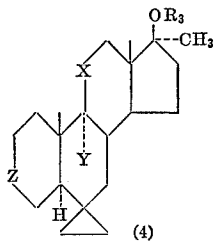
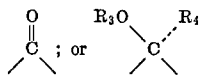
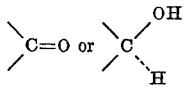


(4)

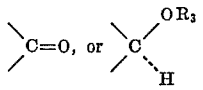
wherein R, R_1 and R_2 are each hydrogen or methyl; R_3 is hydrogen or acyl; W is



in which R_3 has the meaning given above and R_4 is hydrogen or a lower-aliphatic hydrocarbon radical; X is



Y is hydrogen or fluorine; and Z is



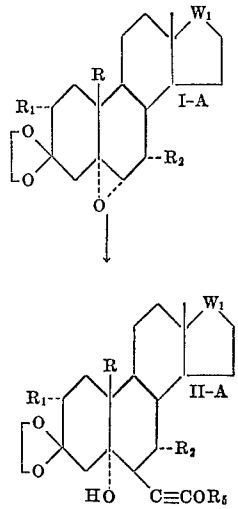
in which R_3 has the meaning given above; to derivatives thereof, to processes for the production of the compounds represented by the above structural formulae and to novel intermediates useful in their production.

The novel compounds of this invention represented by the above structural formulae are anabolic, androgenic, estrogenic, hypocholesteremic, antifertility and progestational agents and are useful for all of the medicinal purposes to which these agents are used, for example, as protein builders, in treatment of atherosclerosis because of their lipid (e.g., chloesterol) normalizing effects, for the treatment of gynecologic disorders, controlling libido, birth control, and for the control of unwanted pests, such as rats, mice, pigeons, starlings, and other rodents and birds, by preventing their procreation.

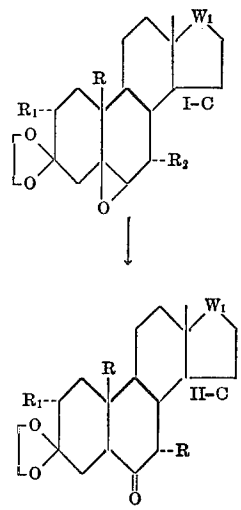
The novel compounds represented by the above structural formulae are useful in the treatment of animals and birds, and are particularly useful in the treatment of humans and valuable domestic animals. They can be administered in conventional dosage forms, such as pills, tablets, capsules, syrups, or elixirs for oral use, or in liquid forms which are suitable for injectable products. They can also be administered topically in the form of ointments, creams, lotions, and the like, with or without coacting antibiotics, germicides or other materials forming advantageous combinations therewith.

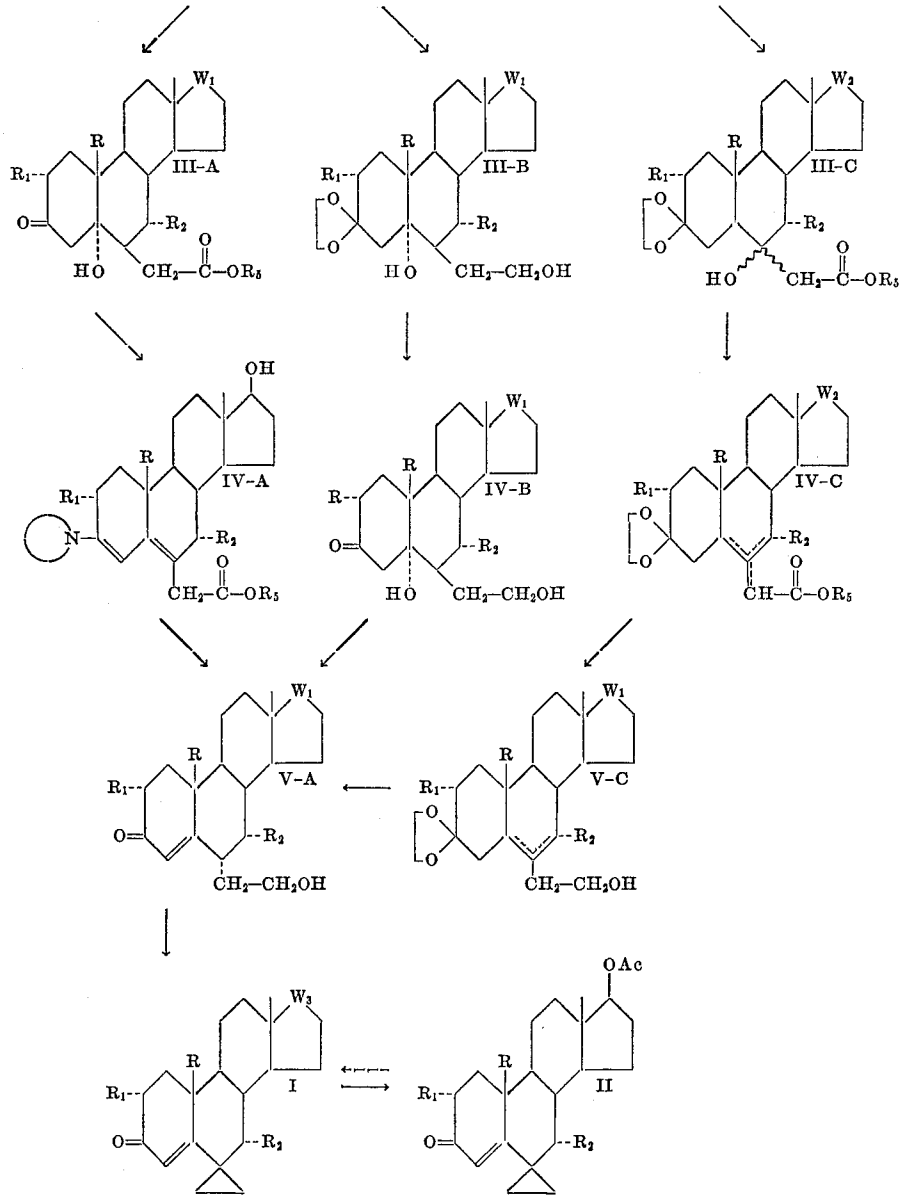
In the process of this invention a 6α-(2'-hydroxyethyl) group is first introduced into the selected androstane, for example a compound of Formula I–A or I–C, by one of three alternative routes designed hereinafter as routes A, B and C. These routes and the compounds produced are represented by the following reaction schemes.

Routes A and B



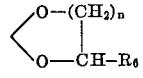
Route C





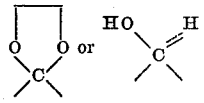
wherein R, R_1, and R_2 have the same meanings as previously given; R_5 is alkyl; the symbol

represents an alkylenedioxy radical of thhe formula



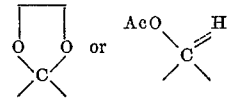
in which *n* is the integer 1 or 2 and R_6 is hydrogen or alkyl; the symbol

is a cyclic amino radical; W_1 is



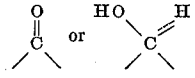
in which the symbol

has the meaning given above; W_2 is



in which the symbol

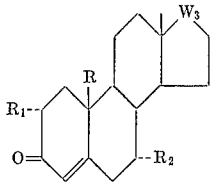
has the meaning given above, and Ac is acyl; and W_3 is



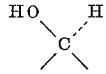
In this application the term "acyl" means the acyl radical of an organic carboxylic acid preferably a hydrocarbon carboxylic acid of 1 to 16 carbon atoms, inclusive, for example, saturated and unsaturated aliphatic acids, and aromatic acids such as acetic, propionic, butyric, isobutyric, tert.-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, dodecanoic, palmitic, acrylic, crotonic, cyclobutanecarboxylic, cyclopentanecarboxylic, cyclopentenecarboxylic, cyclohexanecarboxylic, dimethylcyclohexanecarboxylic, benzoic, toluic, naphthoic, ethylbenzoic, phenylacetic, naphthaleneacetic, phenylvaleric, cinnamic, phenylpropiolic, phenylpropionic, p-butoxyphenylpropionic, succinic, glutaric, dimethylglutaric, maleic, cyclopentylpropionic acids, and the like. The term "lower aliphatic hydrocarbon radical" means a saturated or unsaturated aliphatic hydrocarbon radical containing from 1 to 4 carbon atoms, inclusive, such as alkyl, for example methyl, ethyl, propyl, butyl, and isomeric forms thereof, alkenyl, for example, vinyl, propenyl, butenyl and isomeric forms thereof, and alkynyl, for example, ethynyl, propynyl, butynyl, and isomeric forms thereof. The term "alkyl" means an alkyl radical of one to eight carbon atoms, inclusive, such as methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, and isomeric forms thereof. The term "cyclic amino radical" means a saturated 5 to 9 ring atom cyclic amino radical and is inclusive of pyrrolidino, alkylpyrrolidino such as 2-methylpyrrolidino, 2,2-dimethylpyrrolidino, and the like, piperidino, alkylpiperidino such as 2-methylpiperidino, 3-methylpiperidino, 4,4-dimethylpiperidino and the like, alkylpiperazino such as 4-methylpiperazino and the like, morpholino, alkylmorpholino, such as 2-methylmorpholino, 3-methylmorpholino and the like, hexamethyleneimino, homomorpholino, homopiperidino, thiamorpholino, octamethyleneimino, and the like.

In this application the wavy lines appearing in the structural formulae indicate the α(alpha) configuration, the β(beta) configuration and mixtures thereof.

The 5α,6α-epoxides and 5β,6β-epoxides of Formulae I–A and I–C employed as starting materials in the process of this invention are for the greater part known or can be prepared from known compounds by known methods such as those set forth below and in the preparations appended hereto. Thus the starting materials of Formulae I–A and I–C can be prepared from known compounds of the following formula:



wherein R, R_1, R_2 and W_3 have the meanings previously given, or a 17-acylate thereof when W_3 is



by ketalizing the 3- or 3,17-positions, appropriately, in accordance with methods known in the art, for example Campbell et al., J. Am. Chem. Soc., 80, 4717 (1958) and Bernstein et al., J. Org. Chem., 18, 1166 (1953), to obtain the corresponding Δ^5-3-alkylenedioxy compounds, and the corresponding Δ^5-3,17-bis(alkylenedioxy) compounds. The ketalization reaction is carried out by reacting the selected 3-oxo or 3,17-dioxoandrostene with an alkane-1,2-diol or alkane-1,3-diol such as ethylene, propylene, trimethylene, 1,2-butylene, 2,4-pentylene, 4-methyl-1,2-pentylene, 6-methyl-1,3-hexylene, 1,2-heptylene, 3,4-heptylene, 1,2-octylene glycol and the like; preferably in an organic solvent such as benzene, toluene, xylene, methylene chloride, and the like, and in the presence of an acid catalyst such as p-toluenesulfonic acid, benzenesulfonic acid and the like. The reaction is conducted at a temperature between about 20° C. and about 200° C., preferably between about 70° C. and about 120° C. The time required for the reaction is not critical and may be varied between about 1 and 48 hours, depending on the temperature, the ketalizing agent and catalyst employed.

The alkylenedioxy compounds thus obtained are then epoxidized at the 5,6-positions with a peracid such as perbenzoic, peracetic or perphthalic in accordance with methods known in the art [Campbell et al., J. Am. Chem. Soc., 80, 4717 (1958)] to produce the corresponding 5α,6α- and 5β,6β-expoxides of Formulae I–A and I–C. The reaction is conducted in an inert organic solvent such as tetrahydrofuran, chloroform, methylene chloride, benzene, ether, diglyme, and the like at temperatures from 0 to 100° C. for from about 1 to 80 hours. When the reaction is complete the excess peracid is decomposed and the desired 5,6-epoxides are separated or recovered by conventional methods such as chromatography and/or crystallization.

Thus the corresponding 5α,6α-epoxy and 5β,6β-epoxy compounds of Formulae I–A and I–C can be prepared from the following compounds which are represented by the above formula:

17β-hydroxyandrost-4-ene-3-one,
2α-methyl-17β-hydroxyandrost-4-en-3-one,
7α-methyl-17β-hydroxyandrost-4-en-3-one,
androst-4-ene-3,17-dione,
2α-methyl-androst-4-ene-3,17-dione,
7α-methyl-androst-4-ene-3,17-dione,
17β-hydroxy-19-norandrost-4-ene-3-one,
2α-methyl-17β-hydroxy-19-norandrost-4-en-3-one,
7αmethyl-17β-hydroxy-19-norandrost-4-en-3-one,
19-norandrost-4-ene-3,17-dione,
2α-methyl-19-norandrost-4-ene-3,17-dione,
7α-methyl-19-norandrost-4-ene-3,17-dione,

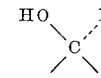
and the corresponding 17β-acylates of the 17β-hydroxy compounds.

ROUTE A

In carrying out the process of Route A of this invention, a 5α,6α-epoxyandrostane of Formula I–A is reacted with an alkoxyacetylene magnesium halide, preferably an alkoxyacetylene magnesium halide in which the alkyl substituent contains from 1 to 8 carbon atoms, inclusive, and more particularly ethoxyacetylene magnesium bromide in accordance with the procedures disclosed in U.S. Pat. 3,088,946 to produce the corresponding 6β-ethynyl-5α-hydroxy compounds of Formula II–A.

The selected 6β-ethynyl-5α-hydroxy compound of Formula II–A is then subjected to hydrolysis in the presence of an acid such as sulfuric, hydrochloric, hydrobromic, perchloric, p-toluenesulfonic, oxalic, acetic and the like in the presence of an inert organic solvent, advantageously a solvent miscible with water such as tetrahydrofuran, acetone, a lower-alkanol, 1,2-dimethoxyethane, dioxane, dimethylformamide and the like to remove the alkylenedioxy groups. The hydrolysis can be carried out within a relatively wide temperature range such as from 0 to 50° C. or higher, however the hydrolysis is advantageously conducted at room temperature, i.e., of the order of 25° C. or at moderately elevated temperatures. The time required for completion of the reaction varies with the temperature employed, a period of from about 3 to 8 hours is generally sufficient at the preferred temperature range. There is thus produced the corresponding 3-oxo-6β-acetic acid alkyl ester of Formula III–A.

The 3-oxo-6β-acetic acid alkyl esters of Formula III–A, wherein W_1 is

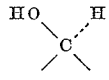


are then reacted with a secondary cyclic amine, pyrrolidine is preferred, in accordance with methods known in the art, e.g., U.S. Pat. 3,070,612, to produce the corre-

sponding 3-enamine (IV–A), which is then treated with a reducing agent to produce the corresponding 6-(2'-hydroxyethyl)-3-enamine, which gives on hydrolysis with an aqueous acid or a base the corresponding 6α-(2'-hydroxyethyl) androst-4-ene of Formula V–A. Suitable reducing agents are lithium aluminum hydride, potassium borohydride, diborane, diisobutyl aluminum hydride, and the like. The preferred reducing agent is lithium aluminum hydride in tetrahydrofuran, etherbenzene, ether, combinations thereof and the like. The reaction is preferably conducted at reflux temperature and a period of 1 to 4 hours is generally sufficient for completion of the reaction.

ROUTE B

In carrying out the process of Route B of this invention a 5α,6α-epoxy androstane of Formula I–A or a 17-acylate thereof when W_1 is



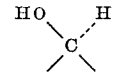
is reacted with an alkoxyacetylene-magnesium halide in the same manner as disclosed in Route A, above, to produce the corresponding 6β-ethynyl-5α-hydroxy compounds of Formula II–A. The latter compounds are then treated with an organic carboxylic acid, preferably a liquid hydrocarbon carboxylic acid containing from 1 to 6 carbon atoms, inclusive, such as formic, acetic, propionic, butyric, isobutyric, and the like. Glacial acetic acid is particularly advantageous. The reaction can be carried out in the presence of an inert solvent, such as ether, methylene chloride, benzene, toluene and the like, or the acid can act as the solvent for the steroid. The reaction is carried out at temperatures from 0 to 80° C., with a temperature of about 25° C. being preferred. The time required for completion of the reaction is from about 1 to 48 hours, depending on the acid and temperature employed. The product is separated from the reaction medium by conventional methods, for example by diluting the reaction mixture with an excess of cold aqueous base, such as sodium or potassium hydroxide, and extracting the product with a water-immiscible organic solvent such as ethyl acetate, methylene chloride, toluene, benzene, Skellysolve B isomeric hexanes and the like. The extract thus obtained is then washed and dried and the solvent removed by evaporation or distillation.

The residual product thus obtained is treated with a reducing agent in the same manner as disclosed in Route A, above, for the conversion of the compounds of Formula IV–A to the compounds of Formula V–A. Lithium aluminum hydride is preferred. There are thus obtained the corresponding 6β-(2'-hydroxyethyl)-5α-hydroxy compounds of Formula III–B.

The compounds of Formula III–B are then subjected to acid hydrolysis in accordance with known methods, for example, under midly acidic conditions at moderate temperatures to remove the alkylenedioxy group or groups giving the corresponding free-oxo compounds of Formula IV–B.

The compounds of Formula IV–B are then subjected to dehydration with a base to produce the corresponding 6α-(2'-hydroxyethyl)-androst-4-ene of Formula V–A. Bases which can be used include sodium or potassium hydroxide, alkali metal alkoxides, e.g., sodium methoxide or ethoxide, alkali earth hydroxides such as barium hydroxide or calcium hydroxide, and the like, in the presence or an inert organic solvent such as methanol, ethanol, dioxane, or other suitable solvents. The alkaline reaction mixture can be allowed to react slowly at room temperature or the mixture can be brought to reflux temperature and refluxed until the reaction is complete, 1 to 30 minutes is usually sufficient.

The 17-acylates of the compounds of Formula I–A, wherein W_1 is



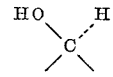
can likewise be used as starting materials in both Routes A and B, above, however, the 17-acylate group is hydrolyzed in each route to the free 17-alcohol during the reduction step if not during the conversion of I–A and II–A.

ROUTE C

In carrying out the process of Route C of this invention a 5β,6β-epoxyandrostane of Formula I–C is dissolved in an inert organic solvent such as benzene, toluene, ethyl ether and the like and treated with boron trifluoride-ethyl ether under anhydrous conditions. The reaction is advantageously carried out at room temperature, i.e., about 25° C. A reaction time of from 1 to 8 hours is usually sufficient for completion of the reaction. The product thus obtained is then separated from the reaction mixture by conventional methods, e.g., the reaction mixture is poured into water and the organic layer separated, washed, dried and concentrated. The product is then treated with a base, in the same manner as disclosed in Route B, above, for the dehydration of the compounds of Formula IV–B to the compounds of Formula V–A to give the corresponding 6-oxo compounds of Formula II–C.

Alternatively the 6-oxo compounds of Formula II–C can be prepared by treating a 5β,6β-epoxide of Formula II–C or the corresponding 5α,6α-epoxide or a mixture of isomeric 5α,6α-and 5β,6β-epoxides with formic acid followed by treatment with a base in accordance with the procedure disclosed by Fried et al., J. Am. Chem. Soc., 81, 1235 (1959).

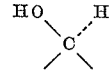
The compounds of Formula II–C wherein W_1 is



are acylated at the 17-position in accordance with methods well known in the art for acylating the 17-hydroxy groups of androstanes, for example, by reaction with the selected acid anhydride or acid halide and by reaction with an acid in the presence of an esterification catalyst. Acylating agents which can be employed are organic carboxylic acids, particularly hydrocarbon carboxylic acids containing from 1 to 16 carbon atoms, inclusive, or acid anhydrides or acid halides thereof, such as those hereinbefore listed. Acylates containing from 2 to 6 atoms are preferred as protecting groups.

A compound of Formula II–C, wherein W_1 is

or acylated



is subjected to a Reformatsky reaction in accordance with methods well known in the art, see for example Organic Reactions, vol. I, pp. 14, 15 and 16, John Wiley and Sons, Inc., New York, N.Y. Thus the selected compound is treated with an alkyl haloacetate such as methyl bromoacetate, or other α-haloester, wherein the alkyl substituent contains from 1 to 8 carbon atoms, inclusive, and the halo substituent is bromine, chlorine, or iodine, in the presence of zinc or magnesium, and in a suitable solvent such as ethyl ether, propyl ether, butyl ether, and the like, or mixtures of these solvents with benzene, toluene, xylene, and the like, to obtain the corresponding 6-carbalkoxymethyl-6-hydroxy compounds of Formula III–C.

The compounds of Formula III–C are then subjected to dehydration with a dehydrating agent, such as thionyl

chloride, N-bromoacetamide in pyridine followed by treatment with sulfur dioxide, phosphorous oxychloride, and the like, to produce the corresponding compounds of Formula IV–C, which comprises a mixture of three isomeric forms, namely, the corresponding androst-5-ene-6-acetic acid alkyl ester, the 5α-androst-6-ene-6-acetic acid alkyl ester and the 5α-androstane-$\Delta^{6,\alpha}$-acetic acid alkyl ester. The isomeric mixture thus obtained can be used in the next step without separation into its various components or if desired the isomers, especially the $\Delta^{6,\alpha}$-isomer can be separated and purified by conventional methods such as chromatography and crystallization.

The Δ^5- and Δ^6-compounds of Formula IV–C are then treated with a reducing agent to obtain the corresponding 6-(2'-hydroxyethyl) compounds of Formula V–C, in the same manner as disclosed in Route A, above, for the conversion of the compounds for Formula IV–A to the compounds of Formula V–A. Lithium aluminum hydride is the preferred reducing agent. The product V–C, thus obtained, comprises a mixture of two isomeric forms of the corresponding 6-(2'-hydroxyethyl) compounds, namely, the corresponding 6-(2'-hydroxyethyl)-androst-5-ene and the corresponding 6-(2'-hydroxyethyl)-5α-androst-6-ene. When a 17-acylate group is present in the compounds of Formula IV–C, it is hydrolyzed to the free 17-alcohol during the reduction.

The compound (V–C) is then subjected to hydrolysis to remove the alkylenedioxy group or groups present in accordance with known methods, such as disclosed in Route B, above, for the hydrolysis of the compounds of Formula III–B to the compounds of Formula IV–B. There are thus obtained the corresponding 6α - (2'-hydroxyethyl)-androst-4-enes of Formula V–A, together with the corresponding 6-(2'-hydroxyethyl)-androst-6-enes as by-products. The desired compounds of Formula V–A are recovered from the reaction mixture by conventional methods such as chromatography and/or crystallization.

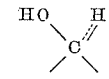
The compounds of Formula V–A obtained by Routes A, B and C, above, are then converted to the Δ^4-3-oxo-6,1'-spirocyclopropanes of Formula I.

The selected 6α-(2'-hydroxyethyl) compounds of Formula V–A are treated with one equivalent of an organic sulfonic acid halide, preferably a hydrocarbon sulfonic acid halide, containing from 1 to 12 carbon atoms, inclusive, generally in the presence of pyridine with or without co-solvents, such as methylene chloride, tetrahydrofuran, benzene, toluene, and the like, in accordance with the procedure disclosed in U.S. Pat. 3,105,083, to produce the corresponding 6α-(2'-organic sulfonyloxyethyl) derivative. Illustrative of organic sulfonic acid halides which can be employed are the acid halides of saturated aliphatic sulfonic acids, such as methanesulfonic, ethanesulfonic, propanesulfonic, butanesulfonic, pentanesulfonic, hexanesulfonic, nonanesulfonic, dodecanesulfonic, 2-propanesulfonic, 2 - butanesulfonic, 2-pentanesulfonic, 2-octanesulfonic, tertiarybutanesulfonic; satuarted cycloaliphatic sulfonic acids, such as cyclopentanesulfonic and cyclohexanesulfonic; aralkyl sulfonic acids such as phenylmethanesulfonic, and phenylethanesulfonic; and aryl sulfonic acids such as benzenesulfonic, o-toluenesulfonic, p-toluenesulfonic, o-bromobenzenesulfonic, p-bromobenzenesulfonic, o-chlorobenzenesulfonic, p-chlorobenzenesulfonic, o-, m-, p-nitrobenzenesulfonic, anisole - 2-sulfonic, anisole-4-sulfonic, and the like. The 6α-(2'-organic sulfonyloxyethyl) derivatives thus obtained can be separated from the reaction medium by conventional methods as hereinbefore disclosed and used directly in the next step or they can be further purified by chromatography or crystallization.

The 6α-(2'-sulfonyloxyethyl) compounds are then subjected to a displacement reaction under basic conditions to effect ring closure at the 6-position. Ring closure is effected under a wide range of conditions and with a wide variety of bases. Illustrative of bases which can be used are alkali metal alkoxides such as potassium tert.-butoxide, sodium methoxide, lithium ethoxide, and the like, sodium or potassium hydroxide in alcohols or aqueous alcohols, secondary amines in alcohols such as pyrrolidine in methanol, alkali earth hydroxides such as barium or calcium hydroxide, and the like. The reaction is advantageously conducted in an organic solvent such as alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, tert.-butanol, and the like; tetrahydrofuran, dioxane or other suitable solvent. When an alkali metal alkoxide is used the reaction is preferably conducted using the corresponding alcohol. There is thereby obtained the corresponding androst-4-ene-6,1'-cyclopropane-3-one of Formula I.

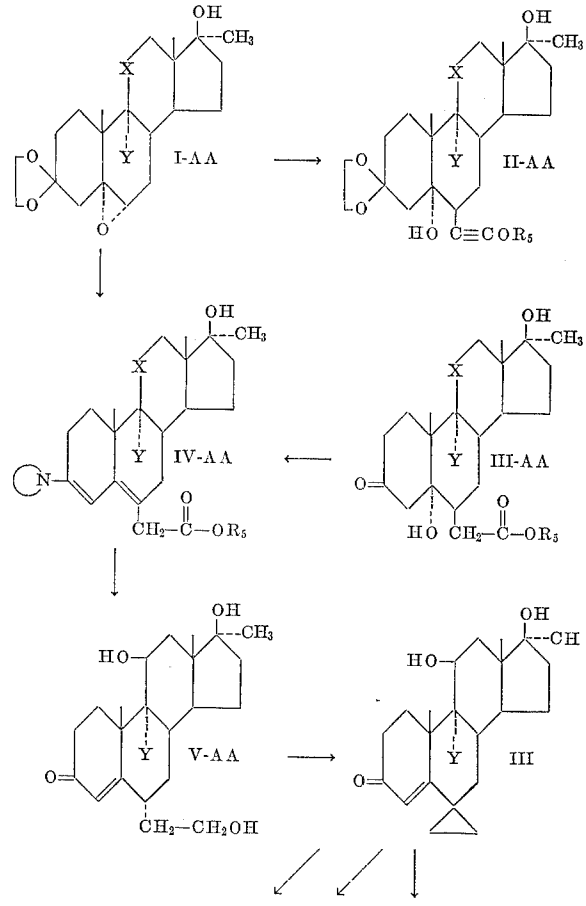
Substituents other than sulfonyloxy such as chlorine, bromine, iodine, quaternary ammonium ions and the like can be used effectively in the displacement reaction. These substituents can be introduced into the 6-(2'-hydroxyethyl) side chain in accordance with known methods.

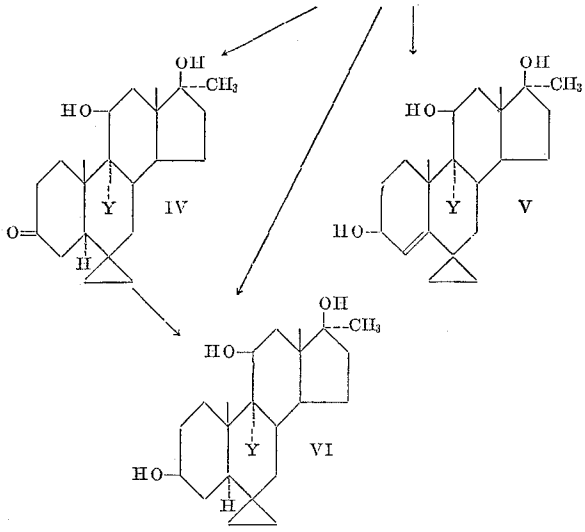
The compounds of Formula I, wherein W_3 is



can be acylated to give the corresponding 17-acylates of Formula II in the same manner as hereinbefore disclosed for acylating the compounds of Formula II–C. Acylating agents which can be employed in the preparation of the above acylates are organic carboxylic acids, particularly hydrocarbon carboxylic acids containing from 1 to 16 carbon atoms, inclusive, such as those acids hereinbefore listed or acid anhydrides or acid halides thereof. The 17β-hydroxy compounds of Formula I can also be esterified at the 17-position in accordance with methods known in the art to produce the corresponding 17β-phosphate and 17β-sulfate esters thereof. See for example Hirschmann et al., Chem. and Ind., 682 (1958) and Butenandt et al., Z. Physiol., 259, 222 (1939).

The compounds of Formulae 3 and 4 of this invention are prepared as illustrated by the following reaction scheme:





wherein X, R_5, the symbol

and the symbol

have the same meanings as previously given; and Y is hydrogen or fluorine.

The 5α,6α-epoxides of Formula I–AA are reacted in accordance with the procedure of Route A, above to introduce a 6α-(2'-hydroxyethyl) group. Thus the selected 5α,6α-epoxide is reacted with an alkoxyacetylene magnesium halide to produce the corresponding 6β-ethynyl-5α-hydroxy compound of Formula II–AA, which is then subjected to hydrolysis in the presence of an acid to produce the corresponding 3-oxo-6β-acetic acid alkyl ester (III–AA). The latter compound is then reacted with a secondary cyclic amine to give the corresponding 3-enamine (IV–AA). The enamine thus obtained is then treated with a reducing agent to produce the corresponding 6-(2'-hydroxyethyl) - 3 - enamine (when an 11-oxo group is present it is concomitantly reduced to an 11β-hydroxy group) which gives on hydrolysis the corresponding 6α-(2' - hydroxyethyl)-androst - 4 - ene of Formula V–AA.

The compounds of Formula V–AA thus obtained are then treated with an organic sulfonyl halide to produce the corresponding 6α-(2'-sulfonyloxy) derivative which is then subjected to a displacement reaction under basic conditions to give the corresponding [androst-4-ene-6,1'-cyclopropane]-3-ones of Formula III.

Substituents other than sulfonyloxy such as those hereinbefore disclosed can also be used effectively in the displacement reaction.

The compounds of Formula III can be reduced to the saturated A-ring compounds of Formula IV in accordance with known methods, for example using hydrogen with a catalyst such as palladium on charcoal or using lithium or sodium in liquid ammonia with or without co-solvents such as ether, tetrahydrofuran, benzene and the like. See Djerassi, Steroid Reactions, Holden-Day, Inc., San Francisco, p. 304 (1963).

The compounds of Formulae III and IV can be reduced in accordance with known methods to obtain the corresponding 3β-hydroxy compounds of Formula VI, for example using sodium borohydride in the presence of pyridine. See Steroid Reactions, supra, page 139.

The compounds of Formula III can also be selectively reduced to the corresponding 3β-hydroxy-Δ^4 compounds of Formula V in accordance with known methods, for example, using lithium aluminum tri-t-butoxyhydride in tetrahydrofuran or with sodium borohydride in an alkanol

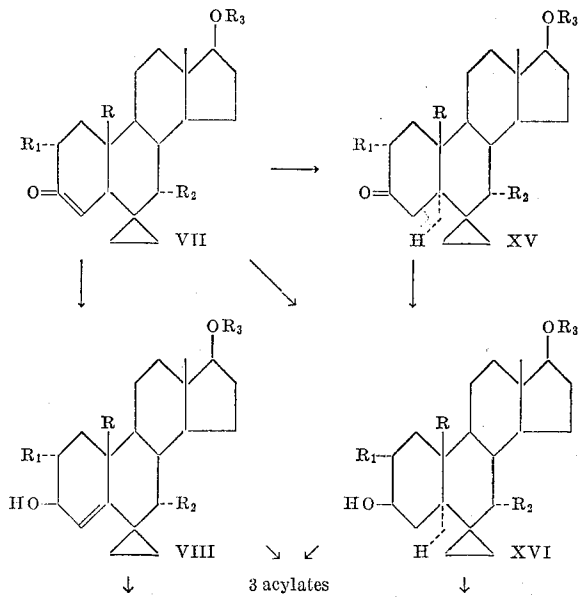
such as ethanol, isopropanol and the like. See Steroid Reactions, supra, page 138.

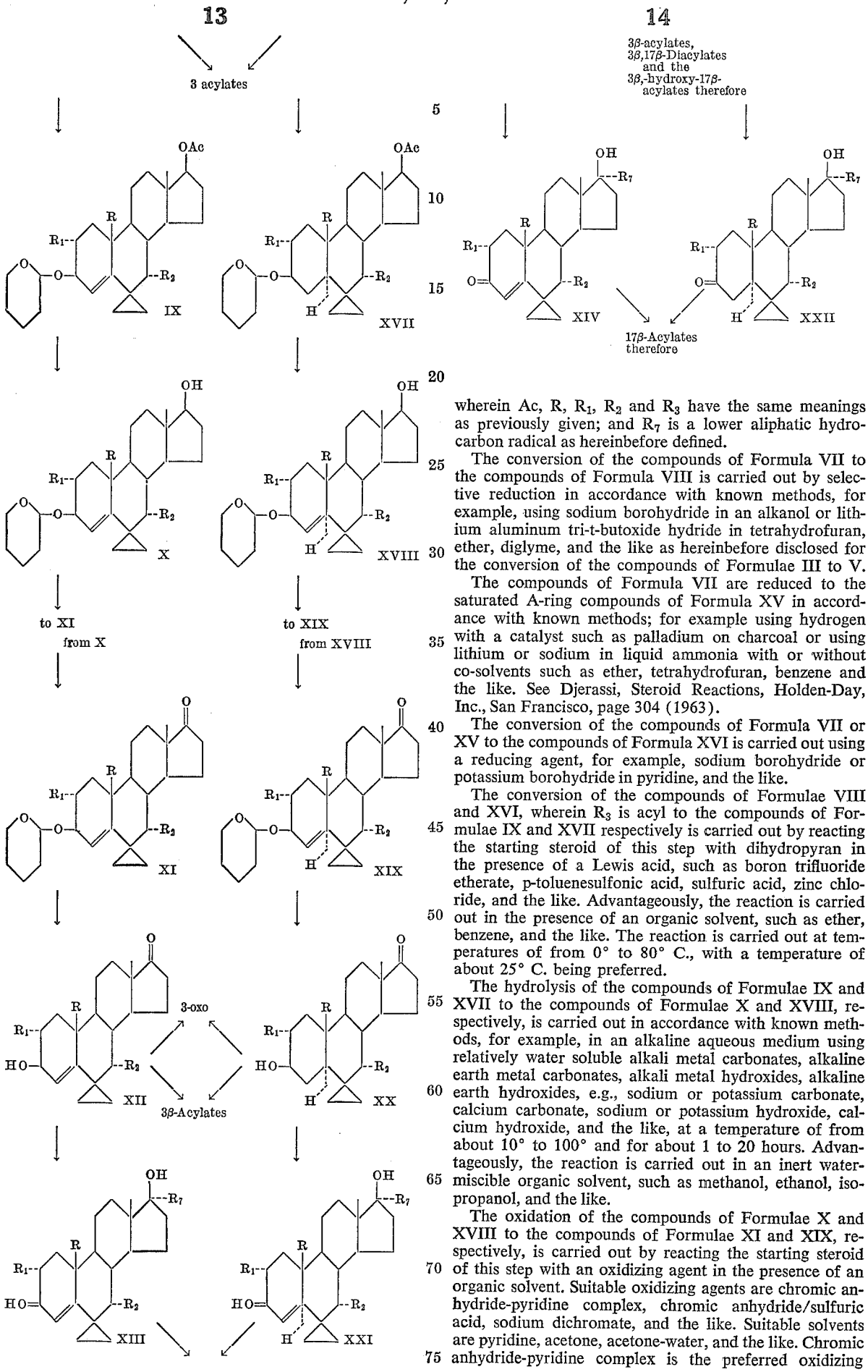
The 11β-hydroxy compounds of Formulae III and IV can be oxidized at the 11-position by known methods for oxidizing 11β-hydroxy groups of steroids, for example with chromic acid, an N-haloamide or N-haloimide, e.g. N-bromoacetamide in pyridine, and the like to give the corresponding 11-oxo compounds.

The compounds of Formulae V and VI can also be oxidized at the 11-position. These compounds are first acylated at the 3-position to protect the 3β-hydroxy group, using mild acylation conditions, for example using an anhydride of an organic carboxylic acid, particularly an anhydride of a hydrocarbon carboxylic acid containing from 1 to 16 carbon atoms, inclusive, such as those acids hereinbefore listed, in the presence of pyridine. The 3β-acylates of V or VI thus obtained are then oxidized at the 11-position in the manner disclosed above to produce the corresponding 3β-acyloxy-11-oxo compounds. These 3β-acylates can, if desired, be hydrolyzed under mildly basic conditions to obtain the corresponding 3β-hydroxy-11-oxo compounds by known methods, for example using aqueous sodium bicarbonate.

The compounds of Formulae III, IV, V and VI, the corresponding 1-oxo compounds and the 3β-acylates of the 3β-hydroxy compounds can be acylated to give the corresponding 17β-acylates in accordance with know methods for acylating the 17β-hydroxy group of 17α-alkylated steroids.' Acylating agents which can be employed in the preparation of the above acylates are organic carboxylic acids, particularly hydrocarbon carboxylic acids containing from 1 to 16 carbon atoms, inclusive, such as those acids hereinbefore listed or acid anhydrides or acid halides thereof, in the presence of an acylation catalyst such as pyridine or with the selected anhydride in the presence of an alkali earth carbonate, such as calcium carbonate. When a 3β-hydroxy group is present as in the compounds of Formulae V and VI and in the corresponding 11-oxo compounds, the corresponding 3β,17β-diacylates will be obtained. When a 3β-acylate group is already present prior to the 17-acylation reaction, mixed esters are obtained in which the acyl radical at the 3-position can be different from that at the 17-position. The 3β,17β-diacylates can be selectively hydrolyzed using a mild base such as sodium bicarbonate to give the corresponding 3β-hydroxy-17β-acylates.

The compounds of Formula I, wherein W_3 is hydroxy, and the compounds of Formula II, represented collectively by Formula VII, below, can be converted to other compounds of this invention in accordance with the following reaction scheme:





wherein Ac, R, R_1, R_2 and R_3 have the same meanings as previously given; and R_7 is a lower aliphatic hydrocarbon radical as hereinbefore defined.

The conversion of the compounds of Formula VII to the compounds of Formula VIII is carried out by selective reduction in accordance with known methods, for example, using sodium borohydride in an alkanol or lithium aluminum tri-t-butoxide hydride in tetrahydrofuran, ether, diglyme, and the like as hereinbefore disclosed for the conversion of the compounds of Formulae III to V.

The compounds of Formula VII are reduced to the saturated A-ring compounds of Formula XV in accordance with known methods; for example using hydrogen with a catalyst such as palladium on charcoal or using lithium or sodium in liquid ammonia with or without co-solvents such as ether, tetrahydrofuran, benzene and the like. See Djerassi, Steroid Reactions, Holden-Day, Inc., San Francisco, page 304 (1963).

The conversion of the compounds of Formula VII or XV to the compounds of Formula XVI is carried out using a reducing agent, for example, sodium borohydride or potassium borohydride in pyridine, and the like.

The conversion of the compounds of Formulae VIII and XVI, wherein R_3 is acyl to the compounds of Formulae IX and XVII respectively is carried out by reacting the starting steroid of this step with dihydropyran in the presence of a Lewis acid, such as boron trifluoride etherate, p-toluenesulfonic acid, sulfuric acid, zinc chloride, and the like. Advantageously, the reaction is carried out in the presence of an organic solvent, such as ether, benzene, and the like. The reaction is carried out at temperatures of from 0° to 80° C., with a temperature of about 25° C. being preferred.

The hydrolysis of the compounds of Formulae IX and XVII to the compounds of Formulae X and XVIII, respectively, is carried out in accordance with known methods, for example, in an alkaline aqueous medium using relatively water soluble alkali metal carbonates, alkaline earth metal carbonates, alkali metal hydroxides, alkaline earth hydroxides, e.g., sodium or potassium carbonate, calcium carbonate, sodium or potassium hydroxide, calcium hydroxide, and the like, at a temperature of from about 10° to 100° and for about 1 to 20 hours. Advantageously, the reaction is carried out in an inert water-miscible organic solvent, such as methanol, ethanol, isopropanol, and the like.

The oxidation of the compounds of Formulae X and XVIII to the compounds of Formulae XI and XIX, respectively, is carried out by reacting the starting steroid of this step with an oxidizing agent in the presence of an organic solvent. Suitable oxidizing agents are chromic anhydride-pyridine complex, chromic anhydride/sulfuric acid, sodium dichromate, and the like. Suitable solvents are pyridine, acetone, acetone-water, and the like. Chromic anhydride-pyridine complex is the preferred oxidizing

agent. The reaction is carried out at temperatures of about 0° to 50° C. for about 2 to 20 hours.

The removal of the tetrahydropyranyl ether group is carried out by treating the compounds of Formulae XI and XIX with an acid in the presence of an organic solvent to obtain the compounds of Formulae XII and XX, respectively. Preferably the acid is a mineral acid, such as hydrochloric, hydrobromic, sulfuric acids, and the like. Suitable solvents are acetone-water, methanol-water, dimethylsulfoxide-water, dimethylformamide-water, and the like. The reaction is conveniently carried out at a temperature of 10° to 50° C. for from about 5 to 50 hours.

The 17-oxo compounds of Formulae XII and XX are then treated with an appropriate alkylating agent such as the appropriate Grignard reagent, alkyl or alkenyl lithium compound or alkali metal alkyne derivative to obtain the compounds of Formulae XIII and XXI, respectively. For example, the 17-oxo compounds (XII or XX) can be reacted with the appropriate alkyl, alkenyl, or alkynyl magnesium halide in the presence of a solvent such as diethyl ether, tetrahydrofuran, benzene and the like, to produce the corresponding compounds of Formulae XIII and XXI, wherein R_7 is alkyl, alkenyl or alkynyl as hereinbefore defined. Preferably, the Grignard reagent is employed in an excess of the order of about 5 to 10 moles per mole of steroid.

Alternatively, the alkylating agent employed to convert XII and XX to the corresponding 17-alkylated compounds XIII and XXI, respectively, in the case where R_7 is alkyl or alkenyl, can be the appropriate alkyl or alkenyl lithium compound. The reaction is conducted advantageously in the presence of an inert solvent such as ether, benzene, toluene, and the like. The lithium compounds are employed advantageously in excess of the stoichiometric proportion and are employed preferably in an amount of at least 2.5 moles per mole of steroid. The reaction is ordinarily conducted at room temperature but may also be conducted at elevated temperatures up to the boiling point of the solvent employed.

The compounds having the Formulae XIII and XXI, wherein R_7 represents a 2 to 4 carbon atom alkynyl group can also be prepared by reacting compounds XII or XX with an alkali metal derivative, for example, the sodium or potassium derivative of the corresponding alkyne. The reaction is carried out preferably in the presence of an inert solvent such as dimethylformamide or dimethylsulfoxide.

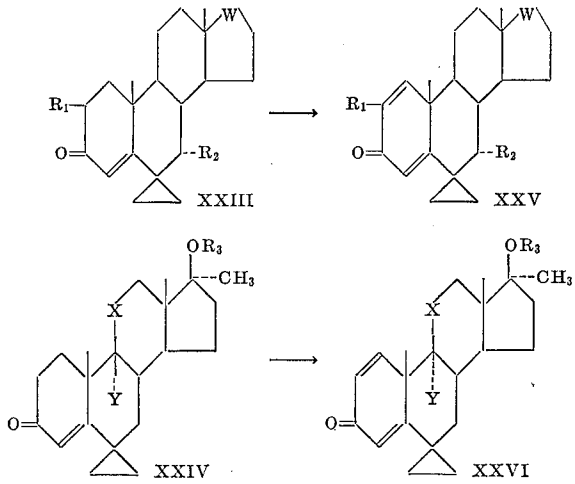
The compounds of Formulae XIII and XXI can be oxidized to the compounds of Formulae XIV and XXII, respectively, by treatment with an oxidizing agent in accordance with known methods, for example, using manganese dioxide in chloroform, chromium trioxide in pyridine, chromic acid in acetone and the like. See for example Djerassi, Steroid Reactions, Holden-Day, Inc., San Francisco (1963), pages 104–118.

The compounds of Formulae XII and XX can likewise be oxidized in the manner disclosed above, to give the corresponding 3-oxo compounds.

The compounds of Formulae VIII, XVI, XII, XX, XIII and XXI can be acylated at the 3-position using mild acylation conditions known in the art for acylating secondary hydroxy groups in steroids as hereinbefore disclosed.

The compounds of Formulae XIII, XXI, XIV and XXII and the 3-acylates of XIII and XXI can be acylated at the 17-position in accordance with methods known in the art for acylating tertiary hydroxy groups of steroids as hereinbefore disclosed. The compounds of Formulae XIII and XXI will be concomitantly acylated at the 3-position to give the corresponding 3,17-diacylates.

The 3-oxo-Δ^4 compounds of this invention represented collectively by Formulae XXIII and XXIV, below, exclusive of the 19-nor compounds, can be dehydrogenated at the 1,2-position by fermentation or chemical dehydrogenation to give the corresponding $\Delta^{1,4}$ compounds of Formulae XXV and XXVI, respectively.

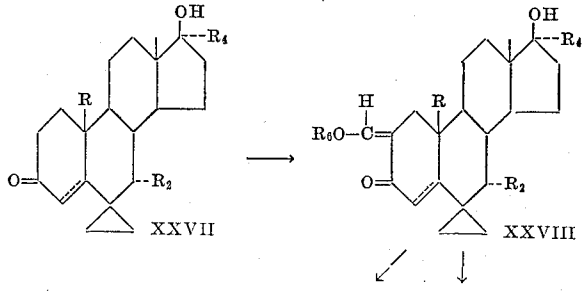


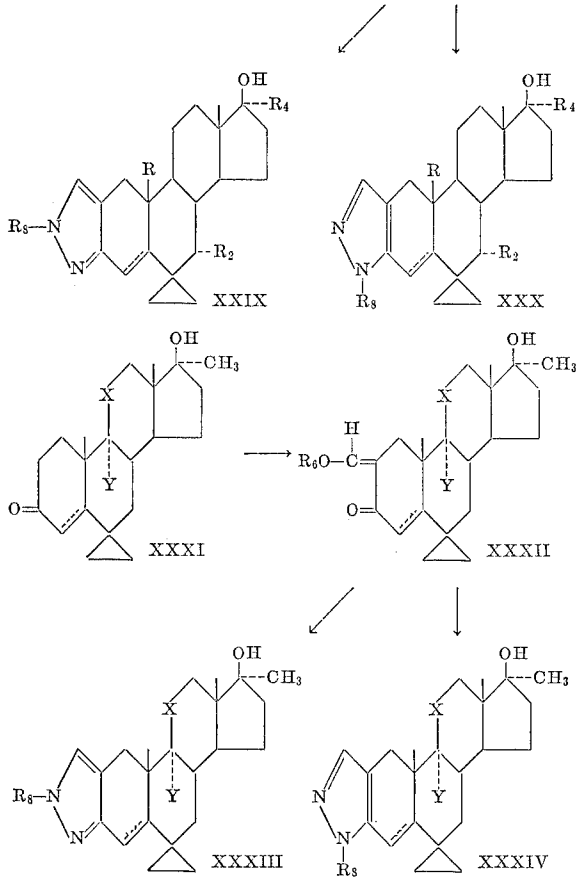
wherein R_1, R_2, R_3, X, Y and W have the same meanings as hereinbefore given.

The novel compounds of Formulae XXV and XXVI are anabolic, androgenic, hypocholesteremic, antifertility and progestational agents, which can be used and administered as hereinbefore disclosed for other compounds of this invention having similar activities.

Fermentative dehydrogenation comprises the use of microorganisms such as Septomyxa, Corynebacterium, Fusarium, and the like, under fermentation conditions well known in the art (e.g., U.S. 2,602,769; 2,902,410 and 2,902,411). Where Septomyxa is used to effect the dehydrogenation it is found to be adavntageous to use with the substrate and medium a steroid promoter. The free alcohols are usually employed as starting material for the fermentative dehydrogenation process. However, the corresponding 17-acylates can be used. In these cases the 17-ester group is generally hydrolyzed during the fermentation process giving the corresponding free alcohols (XXV) and XXVI. The free alcohols can be acylated in the same manner as previously disclosed for acylating the corresponding Δ^4-compounds. Chemical dehydrogenation can be carried out with selenium dioxide according to known procedures, see for example Meystre et al., Helv. Chim. Acta, 39, 734 (1956) or with 2,3-dichloro-5,6-dicayno-1,4-benzoquinone in a suitable organic solvent such as dioxane or benzene, see for example Djerassi, Steroid Reactions, Holden-Day, Inc., San Francisco (1963), p. 232. The 17-acylates are generally preferred as starting materials in the selenium dioxide dehydrogenation reaction giving the corresponding $\Delta^{1,4}$-compounds of Formulae XXV and XXVI. The 17-acylates thus obtained can be saponified, if desired, by methods known in the art to give the corresponding 17-free alcohols.

The 3-oxo compounds of this invention, except those having a methyl group attached at the 2-position and those having a Δ^1-bond, represented collectively by Formulae XXVII and XXXI, below, can be converted to the corresponding pyrazole substituted A-ring compounds in accordance with the following reaction schemes:





wherein, R, R_2, R_4, R_6, X and Y have the same meanings as previously given; R_8 is hydrogen, acyl, alkyl, cycloalkyl, aralkyl, aryl, heterocyclic nucleus, or substituted derivatives thereof, and the dotted line appearing between carbon atoms 4 and 5 represents a single bond linkage or a double bond linkage in which when a single bond linkage is present the configuration of the hydrogen attached at the 5-position is α(alpha).

The terms "acyl" and "alkyl" used above have the same meanings as previously given. The term "cycloalkyl" means a cycloalkyl radical of 3 to 8 carbon atoms, inclusive, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "aralkyl" means an aralkyl radical of 7 to 13 carbon atoms, inclusive such as benzyl, phenethyl, phenylpropyl, benzhydryl, and the like. The term "aryl" means an aryl radical of 6 to 12 carbon atoms, inclusive, such as phenyl, tolyl, xylyl, naphthyl, diphenyl, halophenyl, such as p-fluorophenyl, nitrophenyl, and the like. The term "heterocyclic nucleus" means a ring system of from 4 to 9 carbon atoms, inclusive, containing at least one substituent selected from the group consisting of nitrogen, sulfur and oxygen, such as 2 - pyridyl, 3-pyridyl, 3-pyrimidyl, 3-pyrimidyl, 3-quinolyl, 4-quinolyl, 2-morpholinyl, 2-thiomorpholinyl, 2-pyranyl, 3-thiophenyl, 2-furyl, 2-indolyl and the like.

The pyrazoles of Formulae XXIX and XXXIII are [3,2-c]-pyrazoles whereas those of Formulae XXX and XXXIV are [2,3-d]-pyrazoles. The compounds represented by Formulae XXIX and XXX, and XXXIII and XXIV, where in R_8 is hydrogen, undergo rapid equilbration in solution. Hereinafter, for the sake of simplicity, these resulting mixtures of [2,3-d] and [3,2-c] pyrazoles will be referred to as [2,3-d] pyrazoles.

The novel pyrazoles of Formulae XXIX, XXX, XXXIII and XXXIV, and the novel intermediates XXVIII and XXXII are anabolic, androgenic, hypocholesteremic, antifertility and progestational agents which can be used and administered as hereinbefore disclosed for the other compounds of this invention having similar activities.

The pyrazoles of this invention are prepared in accordance with procedures well known in the art. See for example U.S. Pats. 3,116,287 and 3,067,194 and Clinton et al., J. Am Chem. Soc., 1478–1491 (1961).

The compounds of Formulae XXVII and XXXI are treated with an alkyl formate and sodium hydride in an inert atmosphere to produce the corresponding 2-hydroxymethylene compounds of Formulae XXVIII and XXXII, respectively. The 2-hydroxymethylene compounds thus produced are then treated with a lower-alkanol in the presence of an acidic reagent such as p-toluenesulfonic acid to give the corresponding 2-alkoxymethylene derivatives. The 2-hydroxymethyl compounds, or the 2-alkoxymethylene derivatives thereof, are then reacted with hydrazine or a monosubstituted hydrazine to give the corresponding pyrazoles of Formulae XXIX and XXX, and XXXIII and XXXIV, respectively, which can be separated by conventional methods such as chromatography and/or crystallization.

Representative monosubstituted hydrazines which can be used to prepare the pyrazoles of this invention are: alkylhydrazines, such as methylhydrazine, ethylhydrazine, propylhydrazines, butylhydrazines, β-hydroxyethylhydrazine, cycloalkylhydrazines; arylhydrazines including phenylhydrazine and the substituted phenylhydrazines, such as o-, m-, and p-halophenylhydrazines, o-, m-, and p-tolylhydrazines, o-, m-, and p-alkoxyphenylhydrazines, o-, m-, and p-nitrophenylhydrazines, 1-hydrazinonaphthalene, 2-hydrazinopyridine, 3-hydrazinopyridine, 4-hydrazinopyridine, 4-hydrazinopyridine oxide, 2-hydrazinopyrimidine; 2 - hydrazinothiophene, 3 - hydrazinothiophene; aralkylhydrazines, such as benzylhydrazine and phenylethylhydrazine and the like.

When the compounds of Formula XXXI, wherein Y is halogen are used as starting materials in the above sequence of reactions the 11-oxo compounds (wherein X is >C=O) are preferred over the 11-hydroxy compounds. There is thereby obtained the corresponding compounds of Formulae XXXIII and XXXIV, wherein X is >C=O and Y is halogen, these 11-oxo-9α-halo compounds can be reduced to the corresponding 11β-hydroxy-9α-halo compounds by known methods, e.g., with sodium borohydride.

The compounds of Formulae XXVIII, XXIX, XXX, XXXII, XXXIII and XXXIV can be acylated at the 17-position in accordance with known 17- acylation methods as hereinbefore disclosed to give the corresponding 17β-acylates. When R_8 is hydrogen the N-acyl-17β-acylates will be concomitantly produced giving compounds wherein the acyl groups orient at R_8 and the 17-position are the same.

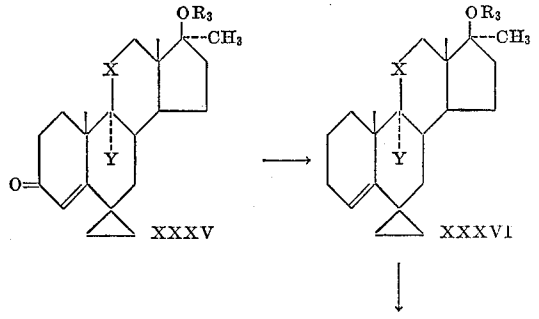
Acyl groups present at R_8 and/or the 17-position can be removed by known methods, for example, by treating the compound with sodium hydroxide in methanol, aqueous alcoholic potassium bicarbonate and the like.

N-acyl groups present at R_8 can be selectively removed by treatment with an aqueous organic acid such as formic acid or acetic acid. The N-unsubstituted 17β-acylates thus obtained can then be reacylated in the same manner as previously disclosed to give compounds wherein the acyl group at R_8 and the 17-position are different.

The pyrazoles of Formulae XXIX and XXX, wherein R_4 is hydrogen, can be oxidized to the corresponding 17-oxo compounds in accordance with methods known in the art, for example, using chromic acid in pyridine or using the Oppenauer oxidation [Djerassi, Steroid Reaction, Holden-Day, Inc., San Francisco, page 98 (1963)].

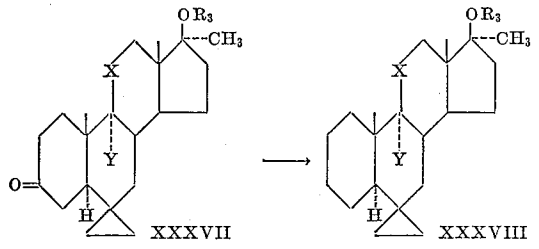
The 3-oxo-Δ^4 and 3-oxo saturated A-ring compounds of this invention which are represented by Formulae XXXV, XXXVII, XXXIX and XLI, below, can be con-

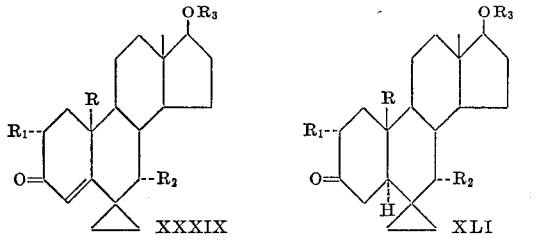
verted to 3-desoxy compounds in accordance with the following reaction schemes:

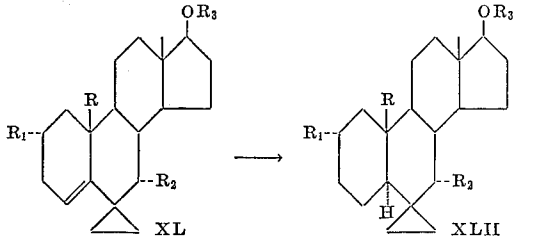


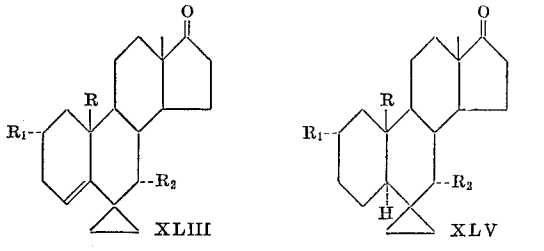
to XXXVIII

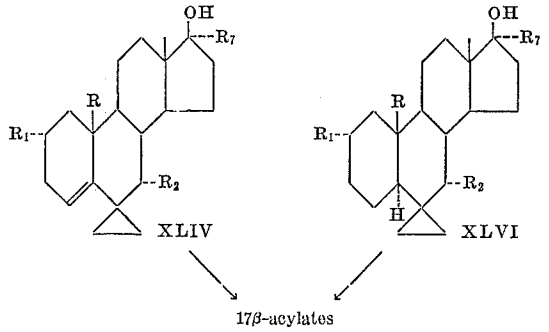
from XXXVI











wherein R, R_1, R_2, R_3, R_7, X and Y have the same meanings as previously given.

The novel 3-desoxy compounds of Formulae XXXVI, XXXVIII, XL, XLII, XLIII, XLIV, XLV and XLVI, and the 17β-acylates of XLIV and XLVI are anabolic, androgenic, hypocholesteremic, antifertility and progestational agents which can be used and administered as hereinbefore disclosed for the other compounds of this invention having similar activities.

In preparing the novel 3-desoxy compound of this invention, the compounds of Formulae XXXV, XXXVII, XXXIX and XLI are first converted to their corresponding 3-thioketal derivatives in the manner disclosed in the J. Am. Chem. Soc., 76, 1955, namely, by reaction with an alkanedithiol (such as ethanedithiol) in the presence of an organic acid and a strong Lewis acid catalyst (e.g., boron trifluoride etherate); desulfurization is then accomplished by hydrogenation of the 3-thioketal group with sodium metal in liquid ammonia or with hydrogen in the presence of a catalyst such as Raney nickel to yield the corresponding 3-desoxy compounds of Formulae XXXVI, XXXVIII, XL and XLII, respectively.

Alternatively, the compounds of Formulae XXXVI and XL can be converted to the compounds of Formulae XXXVIII and XLII, respectively, by reduction of the Δ^4-bond using methods known in the art, for example, catalytic hydrogenation using palladium on charcoal.

The compounds of Formulae XL and XLII are converted to the corresponding 17-oxo compounds of Formulae XLIII and XLV in accordance with methods hereinbefore disclosed, for example, the chromic acid oxidation of the compounds of Formulae X and XVII to the compounds of Formulae XI and XVIII, respectively.

The 17-oxo compounds of Formulae XLIII and XLV, thus obtained, are then converted to the corresponding 17β-hydroxy-17α-lower-aliphatic hydrocarbon compounds of Formulae XLIV and XLVI, respectively, using the methods hereinbefore disclosed for the conversion of the compounds of Formulae XII and XX to the compounds of Formulae XIII and XXI, respectively.

The compounds of Formulae XLIV and XLVI, thus obtained, can be acylated at the 17-position in accordance with the 17β-acylation procedures hereinbefore disclosed.

All of the compounds embraced by the above reaction schemes, namely I–A through II, I–B through II, I–C through II, I–AA through VI, VII through XXII, XXIII through XXV, XXIV through XXVI, XXVII through XXX, XXXI through XXXIV, XXXV through XLVI, and derivatives of the above compounds hereinbefore disclosed, can be isolated from their reaction mixtures by conventional means, for example, when a water-miscible solvent is used, by pouring the reaction mixture into water and separating the resulting precipitate by filtration; when a water-immiscible solvent is used, the reaction mixture can be diluted with water and the product can be recovered in the solvent, the water layer can be further extracted with additional solvent, either the same solvent

or another suitable solvent; solvents which can be used include, for example, methylene chloride, ethyl acetate, chloroform, Skellysolve B (hexanes), benzene, toluene, xylene, ethers, mixtures thereof, e.g., Skellysolve B-methylene chloride, and the like. When water is used as the reaction medium, such as in the bioconversion process, the product can be extracted with a water-immiscible solvent such as those listed above.

Additional purification of the products can be accomplished by conventional methods, for example, by elution chromatography from an adsorbent column with a suitable solvent such as acetone, methanol, ethanol, ether, methylene chloride and Skellysolve B (hexanes), mixtures and combinations of these solvents; also by gradient elution chromatography from an adsorbent column with a suitable mixture of solvents, such as methylene chloride-Skellysolve B, acetone-Skellysolve B, and the like.

The following examples illustrate the best mode contemplated by the inventor for carrying out his invention, but are not to be construed as limiting the scope thereof.

EXAMPLE 1

17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one (V–A)

To a stirred solution of 300 ml. of tetrahydrofuran (distilled from lithium-aluminum hydride) and 17.5 g. of redistilled ethoxyacetylene in a nitrogen atmosphere was added 67 ml. of 3 M ethereal methylmagnesiumbromide at such a rate as to prevent the methane produced from boiling off too vigorously. The mixture was then stirred for 90 minutes at room temperature and 200 ml. of benzene containing 7.81 g. of 5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol (I–A) was added. This mixture was stirred under reflux for about 20 hours, cooled, and a solution of 60 g. of ammonium chloride in 1100 ml. of cold water was added. This mixture was then diluted with methylene chloride and filtered. The organic layer in the filtrate was separated, washed with cold dilute ammonium chloride solution, water, dried and concentrated in vacuo. The residue (9 g.) thus obtained was chromatographed on Florisil (synthetic magnesium silicate, hereinafter called Florisil). The column was eluted with Skellysolve B (isomeric hexanes, hereinafter called Skellysolve B) containing increasing proportions of acetone and those fractions of eluate which, on the basis of infrared analysis, were found to contain the desired product were combined and evaporated to dryness. There was thus obtained 6.41 g. of 3-ethylenedioxy-6β-ethoxyethynylandrostane-5α,17β-diol (II–A), M.P. 157–159° C. (dec.); an analytical sample recrystallized from isopropyl alcohol-water melted at 156–158° C. (dec.), $[\alpha]_D$ −67°, c. 0.948 ($CHCl_3$); the infrared spectrum supported the assigned structure.

Analysis.—Calcd. for $C_{25}H_{38}O_5$ (percent): C, 71.74; H, 9.15. Found (percent): C, 71.49; H, 9.10.

A solution of 6.03 g. of 3-ethylenedioxy-6β-ethoxyethynylandrostane-5α,17β-diol in about 100 ml. of tetrahydrofuran and 6 ml. of 10% sulfuric acid (w./v.) was stirred at room temperature for a period of about 6.5 hours and then 75 ml. of 0.5 N sodium bicarbonate solution was added. Most of the tetrahydrofuran was removed in vacuo and the product thus obtained was extracted with methylene chloride and the extract was washed with water, dried and concentrated. Trituration of the residue thus obtained with ether gave 4.05 g. of 5α,17β-dihydroxyandrostan-3-one-6β-acetic acid ethyl ester (III–A), M.P. 173.5–176° C.; an analytical sample recrystallized from methylene chloride-ether melted at 173–175° C.; $[\alpha]_D$ −26°, c. 0.872 ($CHCl_3$), the infrared spectrum supported the assigned structure.

Analysis.—Calcd. for $C_{23}H_{36}O_5$ (percent): C, 70.74; H, 8.78. Found (percent): C, 70.73; H, 9.31.

To a stirred mixture of 5.0 g. of the 5α,17β-dihydroxyandrostane-3-one-6β-acetic acid ethyl ester and 20 ml. of methanol at 55° C. under a nitrogen atmosphere was added in one portion 2.5 ml. of pyrrolidine. The mixture was heated at 60° C. for 5 minutes, cooled and filtered, giving 3.30 g. of the pyrrolidyl enamine of 5α,17β-dihydroxyandrostan-3-one-6β-acetic acid ethyl ester, M.P. 145–148° C. (dec.). Concentration of the filtrate to dryness in high vacuum and trituration of the residue with ether gave 0.44 g. of additional enamine which was combined with the first crop.

The enamine (3.7 g.) in about 50 ml. of benzene was added with stirring to a slurry of 1.7 g. of lithium aluminum hydride in 170 ml. of ether under a nitrogen atmosphere. The mixture was refluxed for 60 minutes, cooled, and 14 ml. of ethyl acetate was added cautiously followed by 12 ml. of water. The mixture was concentrated to a paste in vacuo. A solution of 120 ml. of methanol and 20 ml. of acetic acid was added to the residue thus obtained and the mixture was stirred at 50° C. for a period of about 15 minutes, cooled and a solution of 25 g. of sodium hydroxide in 150 ml. of water was added under a nitrogen atmosphere. The mixture was stirred and heated at 30–35° C. for a period of about 15 minutes. The mixture was then cooled and made slightly acidic with acetic acid before removing most of the methanol in vacuo. The residue thus obtained was cooled, made distinctly acidic with hydrochloric acid and extracted with methylene chloride. The organic extract was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, water, dried, concentrated in vacuo and the residue was chromatographed on Florisil. The column was eluted with Skellysolve B-methylene chloride (1:1) containing increasing proportions of acetone and those fractions of eluate which, on the basis of infrared analysis, were found to contain the desired product were combined and evaporated to dryness in vacuo giving 1.906 g. of 17β-hydroxy-6-(2'-hydroxyethyl)-androst-4-en - 3 - one which can be used directly in the next step. Crystallization of the product thus obtained from aqueous acetone gave a multihydrate of 17β-hydroxy-6-(2'-hydroxyethyl)-androst-4-en-3-one (V–A) containing about 4.77% water by weight, M.P. 103° C. (cloudy) with clearing and bubbling at 151° C.,

$$\lambda_{max.}^{EtOH}$$

243 mμ, ε 14,000. An analytical sample of 17β-hydroxy-6-(2'-hydroxyethyl)-androst-4-en-3-one was dried under reduced pressure at room temperature was found to contain 0.79% water. The analysis reported below is corrected for the water of hydration.

Analysis.—Calcd. for $C_{21}H_{32}O_3$ (percent): C, 75.86; H, 9.70. Found (percent): C, 75.14; H, 10.30.

In the same manner other 17β-hydroxy compounds of Formula I–A and the corresponding 2α-methyl and 7α-methyl derivative thereof such as:

2α-methyl-5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol,
7α-methyl-5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol,
5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
2α-methyl-5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
7α-methyl-5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,

can be substituted as the starting steroid in Example 1 to give:

2α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one,
7α-methyl-17β-hydroxy-6α(2'-hydroxyethyl)-androst-4-en-3-one,
17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one,
2α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one, and
7α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one,

respectively.

EXAMPLE 2

17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one (V–A)

A mixture of 50 ml. of glacial acetic acid, 25 ml. of methylene chloride and 5 g. of 3 - ethylenedioxy - 6β-ethoxyethynylandrostane - 5α - 17β - diol, prepared from 5α,6α - epoxy - 3 - ethylenedioxyandrostan - 17β - ol in accordance with the procedure disclosed in Example 1, is allowed to stand for 18 hours at room temperature. The mixture is poured into 500 ml. of ice and water containing 25 g. of sodium hydroxide and extracted with warm ethyl acetate. The extract is washed with dilute sodium bicarbonate, water, dried and concentrated in vacuo. The residue thus obtained is dissolved in 125 ml. of tetrahydrofuran and added cautiously to 4 g. of lithium aluminum hydride in 400 ml. of ether. The mixture is refluxed for 2 hours and then 80 ml. of 2 N sodium hydroxide is added cautiously. The reaction mixture is then filtered and the solids are washed with warm ethyl acetate. The organic layer of the combined filtrate and wash is then separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue comprising 3 - ethylenedioxy - 6β - (2' - hydroxyethyl)-androstane-5α,17β-diol (III–B).

The residue thus obtained is dissolved in 60 ml. of tetrahydrofuran and 6 ml. of 10% sulfuric acid is added with stirring. The mixture is stirred for about 6 hours and then 75 ml. of 0.5 N sodium bicarbonate solution is added. Most of the tetrahydrofuran is removed in vacuo and the product is extracted with ethyl acetate, the extract is washed with water, dried and concentrated in vacuo to give a residue comprising 5α,17β - dihydroxy-6β-(2'-hydroxyethyl)-androstan-3-one (IV–B).

The residue thus obtained is dissolved in 150 ml. of methanol containing 1 g. of sodium hydroxide and the mixture is refluxed for 2 to 5 minutes, then concentrated in vacuo. The residue is diluted with water and extracted with warm ethyl acetate. The extract is washed with water, dried and concentrated in vacuo. The residue is crystallized from aqueous acetone giving 17β-hydroxy-6α - (2' - hydroxyethyl) - androst - 4 - en - 3 - one (V–A) as a multihydrate.

In the same manner substituting as starting material in Example 2 other 5α,6α-epoxides of Formula I–A in place of 5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol, for example:

2α-methyl-5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol,
7α-methyl-5α,6α-epoxy-3-ethylenedioxyandrostan-17β-ol,
5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
2α,methyl-5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
7α-methyl-5α,6α-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
5α,6α-epoxy-3,17-bis(ethylenedioxy)androstane,
2α-methyl-5α,6α-epoxy-3,17-bis(ethylenedioxy) androstane,
7α-methyl-5α,6α-epoxy-3,17-bis(ethylenedioxy) androstane,
5α,6α-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane,
2α-methyl-5α,6α-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane, and
7α-methyl-5α6α-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane,

there is ultimately obtained the corresponding 2'-hydroxyethyl compounds of Formula V–A:

2α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one,
7α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one,
17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one,
2α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one,
7α-methyl-17β-hydroxy-6α-(2'-hydroxyethyl)-19-norandrost-4-en-3-one,
6α-(2'-hydroxyethyl)-androst-4-ene-3,17-dione,
2α-methyl-6α-(2'-hydroxyethyl)-androst-4-ene-3,17-dione,
7α-methyl-6α-(2'-hydroxyethyl)-androst-4-ene-3,17-dione,
6α-(2'-hydroxyethyl)-19-norandrost-4-ene-3,17-dione,
2α-methyl-6α-(2'-hydroxyethyl)-19-norandrost-4-ene-3,17-dione, and
7α-methyl-6α-(2'-hydroxyethyl)-19-norandrost-4-ene, 3,17-dione,

respectively.

EXAMPLE 3

17β - hydroxy - 6 - (2' - hydroxyethyl) - 5α - androst-6 - ene - 3 - one and 17β - hydroxy - 6 - (2' - hydroxyethyl)-androst-4-en-3-one (V–A)

To a stirred solution of 10.0 g. of 5β,6β-epoxy-3-ethylenedioxyandrostan-17β-ol (I–C) in about 200 ml. of dry benzene and about 200 ml. of anhydrous ether under a nitrogen atmosphere was added rapidly 38 ml. of boron trifluoride-ethyl ether. The mixture was stirred at room temperature for 3.5 hours and then poured into about 1.5 l. of ice and water. The mixture was shaken and the organic layer was separated quickly and washed immediately with sodium bicarbonate solution, water, dried and concentrated in vacuo. The residue was dissolved in 100 ml. of boiling methanol (nitrogen atmosphere) and a solution of 0.5 g. of potassium hydroxide in 1 ml. of water was added. The mixture was refluxed for 2 minutes, cooled slowly and after about 40 minutes it was concentrated in vacuo. The residue was diluted with water and extracted with methylene chloride. The organic extract was washed with water, dried and concentrated in vacuo. Crystallization of the residue from acetone gave 2.65 g. of 3-ethylenedioxy-17β-hydroxyandrostan-6-one (II–C), M.P. 182–183° C. The filtrate was concentrated and the residue thus obtained was chromatographed on Floirsil. The column was eluted with Skellysolve B containing increasing proportions of acetone and those fractions of eluate which, on the basis of infrared absorption analysis, were found to contain the desired material were combined and evaporated to dryness. There was thus obtained after recrystallization from acetone an additional 2.7 g. of the same product, M.P. 180.5–182° C. An analytical sample prepared by recrystallization from acetone-Skellysolve B gave 3-ethylenedioxy-17β-hydroxyandrostan-6-one, M.P. 183.5–184° C.; $[\alpha]_D$ −24°, c. 0.596 ($CHCl_3$); the infrared spectrum confirmed the assigned structure.

Analysis.—Calcd. for $C_{21}H_{32}O_4$ (percent): C, 72.38; H, 9.26. Found (percent): C, 72.10; H, 9.25.

To a solution of 4.9 g. of the 3-ethylenedioxy-17β-hydroxyandrostan-6-one (II–C) in about 30 ml. of anhydrous pyridine was added with stirring 15 ml. of acetic anhydride. The mixture was stirred for about 1 hour and was then allowed to stand overnight at room temperature. The mixture was cooled in an ice-salt bath and 30 ml. of water was added dropwise, keeping the temperature of the mixture below 5° C. The mixture was stirred for an additional period of about 15 minutes, diluted with water and extracted with ether-methylene chloride (2:1). The organic extract was washed with cold dilute hydrochloric acid, water, dilute sodium bicarbonate solution, water, dried and concentrated in vacuo. Crystallization of the residue from acetone-Skellysolve B gave 5.3 g. of 3-ethylenedioxy-17β-acetoxyandrostan-6-one, M.P. 180–182° C.

The above acylation procedure was repeated and the product recovered by diluting the pyridine solution slowly with a large amount of crushed ice. The product was recovered by direct filtration giving a 70% yield of 3-ethylenedioxy-17β-acetoxyandrostan-6-one, M.P. 179–182° C.

Zinc turnings were purified by dipping them briefly in dilute hydrochloric acid, water, acetone and then drying

them in a vacuum oven. A mixture was prepared consisting of 5 g. of these purified zinc turnings, a trace of iodine, 100 ml. of dry benzene and 100 ml. of anhydrous ether under an atmosphere of nitrogen. To this stirred mixture was added 5 g. of the 3-ethylenedioxy-17β-acetoxyandrostan-6-one and 2 ml. of methyl bromoacetate. For the next three 45-minute intervals, 2.5 g. of zinc was added and at the 90-minute interval 2 ml. of methyl bromoacetate was added. The mixture was stirred and refluxed for a total of about 4 hours. It was then cooled and a small amount of acetic acid was added. The solution was decanted from the excess zinc turnings and the zinc was rinsed with ether and benzene. The combined organic solution was washed with dilute acetic acid, water, dilute ammonium hydroxide, water, dried and concentrated in vacuo. The residue thus obtained was chromatographed on Florisil using methylene chloride-Skellysolve B (1:1) containing increasing amounts of acetone as the eluent, and those fractions of eluate which, on the basis of infrared absorption analysis, were found to contain the desired material were combined and evaporated to dryness. There was thus obtained 5.11 g. of 6-carbomethoxymethyl - 3-ethylenedioxy-6,17β-dihydroxyandrostane 17-acetate (III–C), M.P. 234–235° C.; an analytical sample prepared by recrystallization from acetone melted at 238.5–239° C.; the infrared spectrum confirmed the structure.

Analysis.—Calcd. for $C_{26}H_{40}O_7$ (percent): C, 67.21; H, 8.68. Found (percent): C, 66.80; H, 8.47.

To a solution of 12.1 g. of 6-carbomethoxy-3-ethylenedioxy-6,17β-dihydroxyandrostane 17-acetate in about 160 ml. of pyridine at 0° C. was added dropwise with stirring over a 5-minute period, 8.0 ml. of thionyl chloride. The resulting mixture was stirred for about 10 minutes at 0° C. and then poured into about 3 l. of ice and water. The product was collected on a filter, washed with water, and dried. The crude product was recrystallized from Skellysolve B, yielding 8.81 g. of a mixture of 17β-acetoxy-3-ethylenedioxy-androst-5-ene-6-acetic acid methyl ester (IV–C) and 17β-acetoxy-3-ethylenedioxy-5α-androst-6-ene-6-acetic acid methyl ester (IV–C), M.P. 164–165° C., 0.73 g. with M.P. 157.5–159° C. and 0.35 g. with M.P. 155–155.5° C.; a sample recrystallized from Skellysolve B melted at 165.5–168° C.; $[\alpha]_D$ −69°, c. 0.541 ($CHCl_3$); the infrared spectrum confirmed the assigned structure and the NMR spectrum of this substance confirmed it to be a mixture of the Δ^5- and Δ^6-isomers named above.

Analysis.—Calcd. for $C_{26}H_{38}O_6$ (percent): C, 69.93; H, 8.58. Found (percent): C, 70.12; H, 8.75.

The mother liquors (1.9 g.) from the above crystallizations were combined and chromatographed on Florisil using methylene chloride-Skellsolve B (30:70%) containing increasing amounts of acetone as the eluent. Those fractions which showed a single spot (visible in the ultraviolet) on thin-layer chromatography using ethyl acetate-cyclohexane (1:1) were combined and crystallized from aqueous acetone giving 0.61 g. of 17β-acetoxy-3-ethylenedioxy-5α-androstane-$\Delta^{6,a}$-acetic acid methyl ester (IV–C), M.P. 152–153° C., $[\alpha]_D$ −79°, c. 0.904 ($CHCl_3$) and

$$\lambda_{max.}^{EtOH}$$

225 mμ, ε 15,000.

Analysis.—Calcd. for $C_{26}H_{38}O_6$ (percent): C, 69.93; H, 8.58. Found (percent): C, 69.48; H, 8.67.

A solution of 5.0 g. of a mixture of 17β-acetoxy-3-ethylenedioxy-androst-5-ene-6-acetic acid methyl ester and 17β - acetoxy - 3 - ethylenedioxy-5α-androst-6-ene-6-acetic acid methyl ester in about 130 ml. of dry tetrahydrofuran was added dropwise with stirring to a mixture of 1.94 g. of lithium aluminum hydride in 380 ml. of anhydrous ether over a period of about 30 minutes. The mixture was refluxed for 2 hours, cooled and 12 ml. of ethyl acetate was added cautiously followed by 22 ml. of 40% sodium hydroxide solution. The mixture was filtered and the filtrate concentrated in vacuo. The residue thus obtained was crystallized from acetone giving 2.93 g. of a mixture of 3-ethylenedioxy-6-(2′-hydroxyethyl)-androst-5-en-17β-ol (V–C) and 3-ethylenedioxy-6-(2′-hydroxyethyl)-5α-androst - 6 - en - 17β - ol (V–C), M.P. 201–203.5° C.; $[\alpha]_D$ −45°, c. 0.81 ($CHCl_3$); the infrared spectrum supported the assigned structures.

Analysis.—Calcd. for $C_{23}H_{36}O_4$ (percent): C, 73.36; H, 9.64. Found (percent): C, 73.18. H, 9.73.

A mixture of 6.85 g. of a mixture of 3-ethylenedioxy-6-(2′-hydroxyethyl)-androst-5-en-17β-ol and 3-ethylenedioxy-6-(2′-hydroxyethyl)-5α-androst-6-en-17β-ol, 100 ml. of methanol, 20 ml. of water, and 12 ml. of concentrated hydrochloric acid was stirred at room temperature for 2 hours, then diluted with 400 ml. of water, cooled and filtered giving 4.5 g. of 17β-hydroxy-6-(2′-hydroxyethyl)-5α-androst-6-en-3-one, M.P. 170–200° C. Chloroform extraction of the filtrate yielded 0.95 g. of an oil whose infrared spectrum is essentially identical to that of an authentic sample of 17β-hydroxy-6α-(2′-hydroxyethyl)-androst-4-en-3-one (V–A). Crystallization of the oil from aqueous acetone gave 0.85 g. of 17β-hydroxy-6α-(2′-hydroxyethyl)-androst-4-en-3-one as the multihydrate, M.P. 103–120° C. dec.; the infrared spectrum confirmed the structure. The crude Δ^6-isomer above was suspended in 50 ml. of boiling chloroform and the mixture was diluted with 125 ml. of hot ethyl acetate giving 2.15 g. of 17β-hydroxy-6-(2′-hydroxyethyl)-5α-androst-6-en-3-one, M.P. 209–211° C.; infrared spectrum confirmed the structure.

In the same manner, substituting as starting material in Example 3 other 5β,6β-epoxides of Formula I–C in place of 5β,6β-epoxy-3-ethylenedioxyandrostan-17β-ol, for example:

2α-methyl-5β,6β-epoxy-3-ethylenedioxyandrostan-17β-ol,
7α-methyl-5β,6β-epoxy-3-ethylenedioxyandrostan-17β-ol,
5β,6β-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
2α-methyl-5β,6β-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
7α-methyl-5β,6β-epoxy-3-ethylenedioxy-19-norandrostan-17β-ol,
5β,6β-epoxy-3,17-bis(ethylenedioxy)androstane,
2α-methyl-5β,6β-epoxy-3,17-bis(ethylenedioxy) androstane,
7α-methyl-5β,6β-epoxy-3,17-bis(ethylenedioxy) androstane,
5β,6β-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane,
2α-methyl-5β,6β-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane,
and 7α-methyl-5β,6β-epoxy-3,17-bis(ethylenedioxy)-19-norandrostane,

there are ultimately obtained the same respective 2′-hydroxyethyl compounds of Formula V–A, as named in Example 2, above. When the starting material is a 17-ketal, the 17-acylation step is omitted.

EXAMPLE 4

17β-hydroxyspiro[androst-4-ene-6,1′-cyclopropane]-3-one (I)

A homogeneous mixture of 1.90 g. of dried 17β-hydroxy - 6α - (2′-hydroxyethyl)-androst-4-en-3-one (V–A), 50 ml. of methylene chloride, 3 ml. of dry pyridine, and 1.10 g. of p-toluenesulfonyl chloride was allowed to stand at room temperature for about 18 hours. The mixture was diluted with methylene chloride and washed with water, dilute hydrochloric acid, dilute sodium bicarbonate solution, water and dried. A trace of pyridine was added to the organic layer before concentrating it in vacuo to give a residue comprising 17β-hydroxy-6α-(2′-tosyloxyethyl)-androst-4-en-3-one.

The crude tosylate residue thus obtained was dissolved in about 50 ml. of anhydrous t-butyl alcohol and 0.80 g. of potassium t-butoxide was added with stirring under a nitrogen atmosphere. The mixture was warmed to 35–40° C. for about 1.5 hours, cooled and neutralized with acetic acid. The mixture was concentrated in vacuo and

the residue was dissolved in methylene chloride and the organic solution was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, water, dried and concentrated in vacuo. The residue was chromatographed on Florisil. The column was eluted with Skellysolve B-methylene chloride (1:1) containing increasing proportions of acetone and those fractions of eluate which, on the basis of infrared absorption analysis, were found to contain the desired material were combined and evaporated to dryness. There was thus obtained 0.638 g. of 17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one (I). Recrystallization of this material from acetone gave 0.42 g. of 17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one, M.P. 218–219° C., $[\alpha]_D$ +254°, c. 0.59 ($CHCl_3$), $\lambda_{max.}^{EtOH}$ 249 mμ, ε 14,600; the infrared and NMR spectra confirmed the structure.

Analysis.—Calcd. for $C_{21}H_{30}O_2$ (percent): C, 80.21; H, 9.62. Found (percent): C, 79.98; H, 9.65.

Further elution of the column above with about 23% acetone in 1:1 methylene chloride-Skellysolve B gave 0.45 g. of material whose infrared spectrum is consistent for the structural assignment of 6α-(2'-hydroxyethyl)-17β-tosyloxyandrost-4-en-3-one.

In the same manner, substituting as starting material in Example 4, other 6α-(2'-hydroxyethyl) compounds of Formula V–A, for example those listed in Example 2, above, in place of 17β-hydroxy-6α-(2'-hydroxyethyl)-androst-4-en-3-one, is productive of the corresponding 6,1'-spirocyclopropanes of Formula I, such as:

2α-methyl-17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
7α-methyl-17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
2α-methyl-17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
7α-methyl-17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
spiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione,
2α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione,
7α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione,
spiro[19-norandrost-4-ene-6,1'-cyclopropane]-3,17-dione,
2α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3,17-dione, and
7α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3,17-dione,

respectively.

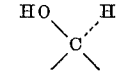
EXAMPLE 5

17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one (II)

A mixture of 450 mg. of 17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one (I), 8 ml. of pyridine, 8 ml. of methylene chloride and 4 ml. of acetic anhydride is stirred overnight at room temperature. The excess anhydride is hydrolyzed by the addition of ice and water and the product is extracted with methylene chloride. The extract is washed with dilute acid, dilute base, water, dried and concentrated in vacuo. The residue thus obtained is chromatographed on 50 g. of silica gel. The column is eluted with chloroform containing increasing proportions of absolute ethanol. The fractions containing the desired product (determined by infrared analysis or thin-layer chromatography) are combined and evaporated to dryness to give 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one.

In the same manner substituting in place of acetic anhydride other acid anhydrides or acid halides of organic carboxylic acids, among which are the hydrocarbon carboxylic acids of from 1 to 16 carbon atoms, inclusive, previously listed, is productive of the corresponding 17α-acyloxy[androst-4-ene-6,1'-cyclopropane]-3-one (II).

In the same manner, following the procedure of Example 5, other compounds of Formula I, wherein W_3 is



for example the 17β-hydroxy compounds prepared and listed in Example 4, are similarly converted to the corresponding 17β-acylates of Formula II, by reacting the selected free 17α-hydroxy compound with the appropriate acid anhydride or acid halide, for example:

2α-methyl-17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one with propionic anhydride to give 2α-methyl-17β-propionyloxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one;
7α-methyl-17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one with hexanoic anhydride to give 7α-methyl-17β-hexanoyloxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one;
17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one with decanoic anhydride to give 17β-decanoyloxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one;
2α-methyl-17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one with succinic anhydride to give 2α-methyl-17β-hemisuccinoyloxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one;
7α-methyl-17β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one with phenylacetic anhydride to give 7α-methyl-17β-phenylacetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,

and the like.

EXAMPLE 6

11β,17β-dihydroxy-17α-methyl - 6α - (2'-hydroxyethyl)-androst-4-en-3-one and 11β,17β-dihydroxy-9α-fluoro-17α-methyl - 6α - (2'-hydroxyethyl)-androst-4-en-3-one (V–AA)

Substituting in Example 1, 5α,6α-epoxy-3-ethylenedioxy-17α-methylandrostane-11β,17β-diol (I–AA) as the starting steroid in place of 5α,6α-epoxy-3-ethylenedioxy-androstan-17β-ol, is productive of 11β,17β-dihydroxy-17α-methyl-6α-(2'-hydroxyethyl)-androst - 4 - en - 3 - one (V–AA).

The corresponding 9α-fluoro compound of Formula I–AA, 5α,6α - epoxy-3-ethylenedioxy-9α-fluoro-17α-methylandrostane-11β,17β-diol can likewise be converted to 11β,17β-dihydroxy - 9α - fluoro - 17α - methyl-6α-(2'-hydroxyethyl)-androst-4-en-3-one (V–AA).

The 11-oxo compounds of Formula I–AA can likewise be used as starting materials in Example 6. However, during the lithium aluminum hydride reaction the 11-oxo-group is reduced to 11β-hydroxy.

EXAMPLE 7

11β,17β-dihydroxy - 17α - methylspiro[androst - 4 - ene-6,1'-cyclopropane]-3-one (III) and 11β,17β-dihydroxy-9α-fluoro - 17α - methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III)

Substituting in Example 4, 11β,17α-dihydroxy-17α-methyl-6α-(2'-hydroxyethyl)-androst-4-ene-3-one or 11β,17α-dihydroxy-9α-fluoro - 17α - methyl-6α(2'-hydroxyethyl)-androst-4-en-3-one as the starting steroid in place of 17β-hydroxy - 6α - (2'-hydroxyethyl)-androst-4-ene-3-one, is productive of 11β,17β-dihydroxy - 17α - methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III) and 11β,17β - dihydroxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III), respectively.

EXAMPLE 8

11β,17β-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV)

A solution of 5.0 g. of 11β,17β-dihydroxy-17α-methylspiro[androst - 4 - ene-6,1'-cyclopropane]-3-one (III) in 190 ml. of 95% ethanol containing 1 g. of 5% palladium on charcoal catalyst is shaken in an atmosphere of hydrogen at about 2 atmospheres pressure. After the approximate theoretical amount of hydrogen has been absorbed, the catalyst is removed by filtration through a bed of diatomaceous earth, and the filtrate is evaporated to dryness at reduced pressure. The residue thus obtained is dissolved in methylene chloride and passed over a column of Florisil. The column is eluted with Skellysolve B containing increasing proportions of acetone and those fractions which by thin-layer chromatography and ultraviolet absorption analysis show the presence of the desired product are taken to dryness and crystallized from a Skellysolve B-acetone to yield 11β,17β-dihydroxy-17α-methylspiro-[5α-androstane-6,1'-cyclopropane]-3-one (IV).

In the same manner substituting 11β,17β-dihydroxy-9α - fluoro - 17α - methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one as the starting steroid is productive of 11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[5α - androstane-6,1'-cyclopropane]-3-one.

EXAMPLE 9

17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI)

To a solution of 2.5 g. of 11β,17β - dihydroxy - 17α-methylspiro[androst - 4 - ene - 6,1' - cyclopropane]-3-one (III) in pyridine is added 1.0 g. of sodium borohydride. After stirring for about 5 hours, acetic acid is added to the reaction mixture until the excess borohydride is destroyed. The crude product is then extracted with methylene chloride. The extract thus obtained is washed with dilute hydrochloric acid, water, dried and chromatographed over a Florisil column packed wet with commercial hexanes. The column is eluted with Skellysolve B containing increasing amounts of acetone and those fractions which by thin-layer chromatographic analysis show the presence of the desired product are taken to dryness and recrystallized from mixtures of acetone-water and acetone-Skellysolve B to yield 17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI).

In the same manner substituting

11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III),
11β,17β-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV) or
9α-fluoro-11β,17β-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV),

as the starting steroid in Example 9 is productive of:

9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI),
17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI) and
9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI),

respectively.

EXAMPLE 10

17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol (V)

To 5 g. of 11β,17β-dihydroxy-17α-methylspiro[androst-4-en-6,1'-cyclopropane]-3-one (III) in 125 ml. of purified tetrahydrofuran, cooled to between 5° C. to −15° C., there is added in small portions with stirring 20 g. of lithium aluminum tri-t-butoxy hydride. The reaction mixture is allowed to gradually come to room temperature and the excess lithium aluminum tri-t-butoxy hydride is destroyed by the addition of dilute acid. A methylene chloride solution of the reaction mixture is washed with dilute hydrochloric acid, water, dried, concentrated somewhat and the residue chromatographed over a Florisil column packed wet with commercial hexanes. The column is eluted with Skellysolve B containing increasing amounts of acetone and those fractions which by thin-layer chromatographic analysis show the presence of the desired product are taken to dryness and recrystallized from mixtures of acetone-water and acetone-Skellysolve B to yield 17α-methylspiro-[androst - 4 - ene - 6,1' - cyclopropane] - 3β,11β,17β-triol (V).

In the same manner, substituting as the starting steroid in Example 10:

11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[androst-4-en-6,1'-cyclopropane]-3-one (III)
11β,17β-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV) or
11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV)

there is obtained:

9-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol (V),
17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI), and
9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI),

respectively.

EXAMPLE 11

3α-acetoxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol

A mixture of 450 mg. of 17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol, 4 ml. of pyridine, 8 ml. of methylene chloride and 1 ml. of acetic anhydride is stirred overnight at room temperature. The excess anhydride is hydrolyzed by the addition of ice and water and the product is extracted with methylene chloride. The extract is washed with dilute acid, dilute base, water, dried and concetntrated in vacuo. The residue is chromatographed on 100 g. of silica gel wet packed in 150 ml. of chloroform and 20 ml. of methanol. The column is eluted with chloroform containing increasing proportions of absolute ethanol and those fractions which by thin-layer chromatographic analysis show the presence of the desired product are taken to dryness and recrystallized from ether to give 3β-acetoxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol.

In the same manner, substituting as the starting steroid in Example 11:

9α-fluoro-17α-mehtylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol,
17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol, or
9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol,

there is obtained:

3β-acetoxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol,
3β-acetoxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol, and
3β-acetoxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol,

respectively.

In the same manner, other 3β-acylates of the above starting steroids such as the 3β-acetate, 3β-butyrate, 3β-valerate, 3β - hexanoate, 3β - trimethylacetate, 3β - isobutyrate, 3β - isovalerate, 3β - cyclohexanecarboxylate, 3β - cyclopentylpropionate, 3β - benzoate, 3β - hemisuccinate, 3β - phenylacetate, 3β - undecylenate, 3β-maleate, 3β-citraconate and the like, can be prepared by substituting in place of acetic anhydride, the appropriate acid anhydrides or acid halides of organic carboxylic acids,

among which are the hydrocarbon carboxylic acids of from 1 to 16 carbon atoms, inclusive, previously listed.

EXAMPLE 12

17β-hydroxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,11-dione

To 300 mg. of 11β,17β - dihydroxy-17α-methylspiro-[androst - 4 - ene - 6,1' - cyclopropane]-3-one (III) in about 5 ml. of pyridine is added a suspension of chromium trioxide pyridine complex (prepared from 300 mg. of chromium trioxide and 5 ml. of pyridine). The reaction mixture is allowed to stand at room temperature until the reaction is complete, a period of about 18 to 24 hours is usually sufficient. Water and methylene chloride (1:1) is then added and the mixture is stirred thoroughly. The organic layer is separated, washed with dilute acid, water, dried over anhydrous sodium sulfate and evaporated in vacuo to remove the solvent giving 17β - hydroxy - 17α - methylspiro[androst - 4-ene - 6,1'-cyclopropane]-3,11-dione, which can be further purified by recrystallization from methylene chloride-Skellysolve B.

In the same manner substituting as the starting steroid in Example 12:

11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III),
11β,17β-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV),
11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV),
3β-acetoxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol (V),
3β-acetoxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol (V),
3β-acetoxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol (VI), or
3β-acetoxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol (VI),

there is obtained:

9α-fluoro-17β-hydroxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,11-dione,
17β-hydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3,11-dione,
9α-fluoro-17β-hydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3,11-dione,
3β-acetoxy-17β-hydroxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11-one,
3β-acetoxy-9α-fluoro-17β-hydroxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11-one,
3β-acetoxy-17β-hydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11-one, and
3β-acetoxy-9α-fluoro-17β-hydroxy-17α-methylspiro-[5α-androstane-6,1'-cyclopropane]-11-one,

respectively.

Other 3β-acylates can be substituted as the starting steroid in Example 12, in place of the 3β-acetates named above, to obtain the corresponding 3β-acyloxy-11-oxo compounds.

EXAMPLE 13

17β-propionyloxy-11β-hydroxy-17α-methylspiro-[androst-4-ene-6,1'-cyclopropane]-3-one

A solution of 2.5 g. of 11β,17β-dihydroxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane] - 3 - one (III), 5 ml. of pyridine and 2.5 ml. of propionic anhydride is heated until the acylation is complete as determined by thin-layer chromatography. Water is then slowly added to the reaction mixture and the product extracted with methylene chloride, washed with dilute sodium hydroxide, saturated sodium chloride solution, dried and the solvent removed. The residue thus obtained is chromatographed on Florisil and eluted with Skellyslove B containing increasing proportions of acetone. Those fractional containing the desired product as determined by thin-layer chromatography are combined, evaporated to dryness and recrystallized from Skellysolve B-acetone to give 17β-propionyloxy-11β-hydroxy - 17α - methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one.

Similarly, other 17β-acylates of 11β,17β - dihydroxy-17α-methylspiro[androst - 4 - ene - 6,1' - cyclopropane] 3-one such as the 17β-acetate, 17β-butyrate, 17β-valerate, 17β-hexanonate, 17β - isobutyrate, 17β - isovalerate, 17β-cyclohexanecarboxylate, 17β-cyclopentylpropionate, 17β-benzoate, 17β-hemisuccinate, 17β-phenylacetate, 17β-undecylenate, 17β-maleate, 17β-citraconate, and the like, can be prepared by reacting the 17-free hydroxy compound with the appropriate acid anhydride or halide of an organic carboxylic acid, among which are the hydrocarbon carboxylic acids of 1 to 16 carbon atoms, inclusive, previously listed.

In the same manner, following the procedure of Example 13 and the paragraph directly hereinabove, but substituting one of the following as the starting steroid therein:

11β,17β-dihydroxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (III),
11β,17α-dihydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV),
11β,17α-dihydroxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (IV),
3β-acyloxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol,
3β-acyloxy-9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-11β,17β-diol,
3β-acyloxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol,
3β-acyloxy-9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-11β,17β-diol,

and the corresponding 11-oxo compounds is productive of the corresponding 17β-acylates thereof.

Similarly, following the procedure of Example 13 and substituting as starting material therein:

17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol (V),
9α-fluoro-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β,17β-triol (V),
17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI),
9α-fluoro-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,11β,17β-triol (VI),

or the corresponding 11-oxo compounds in place of 11β,17β-dihydroxy-17α-methylspiro[androst - 4 - ene - 6,1'-cyclopropane]-3-one, and using an appropriately larger amount of the selected acid anhydride or acid halide is productive of the corresponding 3β,17β-diacylates thereof, such as 3β,17β - dipropionyloxy - 17α - methylspiro [androst-4-ene-6,1'-cyclopropane]-11β-diol, and the like.

EXAMPLE 14

17β-propionyloxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,11β-diol

A mixture comprising 2.0 g. of 3β,17β-dipropionyloxy-17α-methylspiro[androst - 4 - ene - 6,1'-cyclopropane]-11β-ol, 100 ml. of 5% potassium carbonate in methanol-water (4:1) solution is allowed to stand at room temperature until the selective hydrolysis is complete; the progress of the reaction can be followed by thin-layer chromatography, about 18 to 20 hours is usually sufficient. The solvents are then removed under reduced pressure to give a residue comprising 17β-propionyloxy-17α - methylspiro[androst - 4-ene-6,1'-cyclopropane]-3β,11β-dol, which can be further purified by crystallization from a suitable solvent, such as methanol, ethanol, acetone, Skellysolve B-acetone and the like.

In the same manner other 3β,17β-diacylates of 17α-methylspiro[androst-4-ene-6,1' - cyclopropane] - 3β,11β,

17β-triol can likewise be selectively hydrolyzed to remove the 3β-acylate group, to give the corresponding 17β-acyloxy-17α - methylspiro[androst - 4 - ene - 6,1'-cyclopropane]-3β,11β-diol.

Similarly, the other 3β,17β-diacyloxy compounds prepared in Example 13, above, can likewise be selectively hydrolyzed to obtain the corresponding 3β-hydroxy-17β-acyloxy compounds.

EXAMPLE 15

17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII)

To 5 g. of 17β - acetoxyspiro[androst-4-en-6,1'-cyclopropane]-3-one (VII) in 125 ml. of purified tetrahydrofuran, cooled to between 5° C. to −15° C., there is added in small portions with stirring 20 g. of lithium aluminum tri-t-butoxy hydride. The reaction mixture is allowed to gradually come to room temperature and the excess lithium aluminum tri-t-butoxy hydride is destroyed by the addition of dilute acid. The reaction mixture is washed with dilute hydrochloric acid, dried and chromatographed over a Florisil column packed wet with commercial hexanes. The column is eluted with Skellysolve B containing increasing amounts of acetone and those fractions which by thin-layer chromatography and infrared absorption show the presence of the desired product are taken to dryness and recrystallized from mixtures of acetone-water and acetone-Skellysolve B to yield 17β-acetoxyspiro[androst-4 - ene - 6,1' - cyclopropane]-3β-ol (VIII).

In the same manner, substituting other compounds of Formula VII as the starting steroid in place of 17β-acetoxyspiro[androst - 4 - ene - 6,1'-cyclopropane]-3-one, for example:

2α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
7α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
17α-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
2α-methyl-17α-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
7α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,

there is obtained:

2α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
7α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
2α-methyl-17β-acetoxyspiro]19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII), and
7α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII),

respectively.

In the same manner other 17β-acylates of Formula VII, wherein the acyl radical is that of an organic carboxylic acid, preferably a hydrocarbon carboxylic acid containing from 1 to 16 carbon atoms, inclusive, such as those hereinbefore listed, or the corresponding 17β-free hydroxy compounds of Formula VII, can likewise be reduced to the corresponding 3β-hydroxy compounds of Formula VIII.

EXAMPLE 16

17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV)

A solution of 5.0 g. of 17β-acetoxyspiro[androst-4-ene-6,1' - cyclopropane]-3-one (VII) in 190 ml. of 95% ethanol containing 1 gram of 5% palladium on charcoal catalyst is shaken in an atmosphere of hydrogen at 2 atmospheres pressure. After the approximate theoretical amount of hydrogen has been absorbed, the catalyst is removed by filtration through a bed of diatomaceous earth, and the filtrate is evaporated to dryness at reduced pressure. The residue thus obtained is dissolved in methylene chloride and passed over a column of Florisil. The column is eluted with Skellysolve B containing increasing proportions of acetone and those fractions which by thin-layer chromatography and ultraviolet absorption analysis show the presence of the desired product are taken to dryness and recrystallized from Skellysolve B-acetone to yield 17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV).

EXAMPLE 17

17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV)

A solution of 5.0 g. of 17β-acetoxy-17α-methylspiro-[androst-4-ene-6,1'-cyclopropane]-3-one (VII) in about 100 ml. of tetrahydrofuran is poured cautiously into 500 ml. of distilled liquid ammonia. About 2 molar equivalents of lithium metal is then added in small pieces; after about 10 minutes any blue color is discharged by the cautious addition of ammonium chloride. A fast stream of nitrogen is passed through to aid in evaporating the solvents. After nearly all of the ammonia and other solvents are removed, water is added. The resulting precipitate is collected, washed with water, dried and recrystallized from Skellysolve B-acetone to yield 17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV).

In the same manner, substituting other compounds of Formula VII, in place of 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one in Example 16 or 17, for example:

2α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
7α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one,
17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,
2α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one, and
7α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one

there is obtained

2α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV),
7α-methyl-17β-acetoxyspiro[5α-androstone-6,1'-cyclopropane]-3-one (XV),
17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XV),
2α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XV), and
7α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XV),

respectively.

In the same manner, other 17β-acylates of Formula VII, wherein the acyl radical is that of an organic carboxylic acid, preferably a hydrocarbon carboxylic acid containing 1 to 16 carbon atoms, inclusive, such as those herebefore listed or the corresponding 17β-hydroxy compounds of Formula VII, can likewise be reduced to the corresponding saturated A-ring compounds of Formula XV.

EXAMPLE 18

17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI)

To a solution of 2.5 g. of 17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one (XV) in ethanol is added 1.0 g. of sodium borohydride. After stirring for about 5 hours at room temperature, acetic acid is added to the reaction mixture until excess borohydride is destroyed. The crude product is precipitated with water, filtered, washed, dried and recrystallized from acetone-Skellysolve

B to yield 17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XV).

In the same manner, substituting other compounds of Formula XV in place of 17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one, for example:

2α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one,
7α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3-one,
17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one,
2α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one, and
7α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one,

there is obtained

2α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
7α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
2α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI), and
7α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),

respectively.

In the same manner other 17β-acylates of Formula XV, wherein the acyl radical is that of an organic carboxylic acid, preferably a hydrocarbon carboxylic acid containing 1 to 16 carbon atoms, inclusive, such as those hereinbefore listed or the corresponding 17β-hydroxy compounds of Formula XV, can likewise be reduced to the corresponding 3β-hydroxy compounds of Formula XVI.

EXAMPLE 19

17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX)

To 1.8 g. of 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII) in 10 ml. of dihydropyran and 50 ml. of ether, 100 mg. of p-toluenesulfonic acid is added. The ether solution is stirred for about 16 hours, extracted successively with sodium bicarbonate solution, saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to yield 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX). This residue is employed in the following example without further purification.

Similarly substituting an equivalent amount of

2α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
7α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
2α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
7α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol (VIII),
17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
2α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
7α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
2α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),
7α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol (XVI),

yields residues comprising:

2α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX),
7α-methyl-17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX),
17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX),
2α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX),
7α-methyl-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX),
17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII),
2α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII),
7α-methyl-17β-acetoxyspiro[5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII),
17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII),
2α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII), and
7α-methyl-17β-acetoxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β-ol 3-tetrahydropyranyl ether (XVII),

respectively.

EXAMPLE 20

Spiro[androst - 4 - ene - 6,1' - cyclopropane]-3β-17β-diol 3-tetrahydropyranyl ether (X)

The residue comprising 17β - acetoxyspiro[androst-4-ene - 6,1' - cyclopropane]-3β-ol 3-tetrahydropyranyl ether (IX) (obtained in Example 19) is dissolved in 100 ml. of 5% potassium carbonate in methanol-water (4:1) solution and the reaction mixture heated to reflux for about 1.5 hours. The organic solvent is removed under reduced pressure to give a residue comprising spiro[androst-4-ene-6,1'-cyclopropane]-3β-17β-diol 3-tetrahydropyranyl ether (X), which is collected on a filter and washed with water.

In the same manner, substituting in Example 20 the residues comprising the other 17β-acetoxy-3-tetrahydropyranyl ethers listed in the last paragraph of Example 19, above, yields the corresponding residues comprising:

2α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (X),
7α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (X),
spiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (X),
2α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (X),
7α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (X),
spiro[5α-androstane-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (XVIII),
2α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (XVIII),
7α-methylspiro[5α-androstane-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (XVIII),
spiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (XVIII),
2α-methylspiro[19-nor-5α-androstane-6,1'-cyclopropane] - 3β,17β - diol 3 - tetrahydropyranyl ether XVIII), and
7α-methylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3β,17β-diol 3-tetrahydropyranyl ether (XVIII),

respectively.

EXAMPLE 21

3β-hydroxyspiro[androst - 4-ene - 6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XI)

The residue comprising spiro[androst-4-ene-6,1'-cyclopropane]-3β,17β-diol 3-hydropyranyl ether (X) (obtained in Example 20) is taken up in 10 ml. of pyridine and added to pyridine-chromic acid complex prepared from 2

g. of chromic anhydride in 20 ml. of pyridine. The reaction mixture is stirred for about 5 hours at room temperature, diluted with a 1:1 mixture of ether and benzene and filtered on a Celite (diatomaceous earth) pad. The filtrate is washed successively with dilute acid, water, saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to yield a residue comprising 3β-hydroxyspiro [androst-4-ene-6,1'-cyclopropane]-17-one 3 - tetrahydropyranyl ether (XI) which was used without further purification in the following example.

Similarly substituting for the residue comprising spiro [androst-4-ene-6,1'-cyclopropane]-3β-17β - diol the residues comprising the other 17β-free hydroxy-3-tetrahydropyranyl ethers listed in the last paragraph of Example 20, above, yields residues comprising:

2α-methyl-3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XI),
7α-methyl-3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XI),
3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XI),
2α-methyl-3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XI),
7α-methyl-3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane[-17-one 3-tetrahydropyranyl ether (XI),
3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XIX),
2α-methyl-3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XIX),
7α-methyl-3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XIX),
3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XIX),
2α-methyl-3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether (XIX), and
7α-methyl-3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one 3-tetrahydropyranyl ether

respectively.

EXAMPLE 22

3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one (XII)

The residue comprising 3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane] - 17 - one 3-tetrahydropyranyl ether (XI) (obtained in Example 21) is taken up in 20 ml. of acetone and 2 ml. of acetone and 2 ml. of 3 N hydrochloric acid added thereto. The reaction mixture, after standing at room temperature overnight is diluted with water, extracted with methylene chloride and the organic extract is washed with water, dilute base, water, dried and concentrated. The residue is chromatographed on a column of Florisil. The column is eluted with Skellysolve B containing increasing amounts of acetone and those fractions which by thin-layer chromatography and ultraviolet absorption show the presence of the desired product are taken to dryness and crystallized from acetone to give 3β-hydroxyspiro[androst - 4 - ene-6,1'-cyclopropane]-17-one (XII).

Following the procedure of Example 22, but substituting for the residue comprising 3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane] - 17 - one 3-tetrahydropyranyl ether the residues comprising the other 17-oxo-3-dihydroxypyranyl ethers listed in the last paragraph of Example 21, yields:

2α-methyl-3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one (XII),
7α-methyl-3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one (XII),
3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-17-one (XII),
2α-methyl-3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-17-one (XII),
7α-methyl-3β-hydroxyspiro[19-norandrost-4-ene-6,1'-cyclopropane]-17-one (XII),
3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one (XX),
2α-methyl-3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one (XX),
7α-methyl-3β-hydroxyspiro[5α-androstane-6,1'-cyclopropane]-17-one (XX),
3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one (XX),
2α-methyl-3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one (XX), and
7α-methyl-3β-hydroxyspiro[19-nor-5α-androstane-6,1'-cyclopropane]-17-one (XX),

respectively.

EXAMPLE 23

Spiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione

To 300 mg. of 3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one (XII) in about 5 ml. of pyridine is added a suspension of chromium trioxide pyridine complex (prepared from 300 mg. of chromium trioxide and 5 ml. of pyridine). The reaction mixture is allowed to stand at room temperature until the reaction is complete, a period of about 10 to 24 hours is usually sufficient. Water and methylene chloride (1:1) is then added and the mixture is stirred thoroughly. The organic layer is separated, washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo to remove the solvent, giving spiro[androst - 4 - ene-6,1'-cyclopropane] 3,17-dione, which can be further purified by recrystallization from methylene chloride-Skellysolve B.

In the same manner, substituting as the starting steroid in Example 23, the other 3β-hydroxy-17-oxo compounds of Formulae XII and XX, listed in the last paragraph of Example 22, above, yields:

2α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione,
7α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3,17-dione,
spiro[19-norandrost-4-ene-6,1'-cyclopropane]-3,17-dione,
2α-methyl-spiro[19-norandrost-4-ene-6,1'-cyclopropane] 3,17-dione,
7α-methyl-spiro[19-norandrost-4-ene-6,1'-cyclopropane] 3,17-dione,
spiro[5α-androstane-6,1'-cyclopropane]3,17-dione,
2α-methyl-spiro[5α-androstane-6,1'-cyclopropane]3,17-dione,
7α-methyl-spiro[5α-androstane-6,1'-cycloporpane]-3,17-dione,
spiro[19-nor-5α-androstane-6,1'-cyclopropane]-3,17-dione,
2α-methyl-spiro[19-nor-5α-androstane-6,1'-cyclopropane]-3,17-dione, and
7α-methyl-spiro[19-nor-5α-androstane-6,1'-cyclopropane-3,17-dione,

respectively.

In the same manner, the corresponding 17β-hydroxy-3-ones, such as 17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one and the like, can be substituted as starting material in place of the 3β-hydroxy-17-ones in Example 23, to obtain corresponding 3,17-diones, such as spiro[androst-4-ene-6,1'-cyclopropane] - 3,17-dione and the others named in the immediately preceding paragraph.

EXAMPLE 24

17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,17β-diol (XIII)

A solution of 2.75 g. of 3β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-17-one (XII) in 70 ml. of tetrahydrofuran is added over a short period with stirring under an atmosphere of nitrogen to 25 ml. of a 3 M solu-

tion of methylmagnesium bromide in diethyl ether. The resulting mixture is heated under reflux for approximately 4 hours. To the mixture so obtained is added carefully with stirring an iced ammonium chloride solution followed by 130 ml. of methanol and 25 ml. of 5% aqueous sodium hydroxide. The mixture is stirred at 40° C. under nitrogen for several hours and is concentrated to about one-third volume under reduced pressure. The resulting mixture is diluted with water and extracted with ether. The ether extract is washed successively with water, dilute hydrochloric acid, dilute aqueous sodium carbonate, and water before being dried over anhydrous sodium sulfate and filtered. The filtrate is evaporated to dryness and the residue is dissolved in methylene chloride and chromatographed over 200 g. of Florisil. The column is eluted with Skellysolve B containing increasing proportions of acetone and those fractions of the eluate which on infrared absorption analysis show no C–17 carbonyl absorption are combined and evaporated to dryness. The residue is recrystallized from a mixture of acetone and Skellysolve B. There is thus obtained 17α-methylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII).

In the same manner, substituting as the starting steroid in Example 24 other compounds of Formulae XII and XX in place of 3β-hydroxyspiro[androst-4-ene-6,1′-cyclopropane]17-one, for example those prepared and listed in the last paragraph of Example 22, above, yields:

2α,17α-dimethylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII),
7α,17α-dimethylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII),
17α-methylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
2α,17α-dimethylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
7α,17α-dimethylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
17α-methylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
2α,17α-dimethylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
7α,17α-dimethylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
17α-methylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
2α,17α-dimethylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI), and
7α,17α-dimethylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),

respectively.

Using the procedure of Example 24 but replacing methyl-magnesium bromide by ethyl magnesium bromide, propylmagnesium bromide, isopropylmagnesium bromide, butylmagnesium bromide, allylmagnesium bromide, vinyl magnesium bromide, propenyl magnesium bromide, isopropenyl magnesium bromide, and 2-butynyl bromide, and the like, there are obtained the corresponding 17α-ethyl, 17α-propyl, 17α-isopropyl, 17α-butyl, 17α-allyl, 17α-vinyl, 17α-propenyl, 17α-isopropenyl and 17α-methallyl, compounds of Formulae XIII and XXI, and the like.

EXAMPLE 25

17α-ethynylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII)

A volume of 2 ml. of a 20 percent by weight suspension of sodium acetylide in xylene is centrifuged and the solid which separated is taken up in 10 ml. of redistilled dimethylformamide. To the resulting mixture is added 0.5 g. of 3β - hydroxyspiro[androst - 4 - ene-6,1′-cyclopropane]-17-one. The mixture so obtained is maintained under an atmosphere of nitrogen for about five hours at the end of which time the excess sodium acetylide is destroyed by dropwise addition of water. The mixture so obtained is extracted with ether and the ethereal extract is washed successively with dilute hydrochloric acid, dilute sodium carbonate and water before being dried over anhydrous magnesium sulfate. The dried solution is filtered and the filtrate is evaporated to dryness. The residue is triturated with a mixture of ether and Skellysolve B and recrystallized twice from a mixture of acetone and Skellysolve B. There is thus obtained 17α-ethynylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII).

In the same manner, substituting as the starting steroid in Example 25 other compounds of Formulae XII and XX in place of 3β-hydroxyspiro[androst-4-ene-6,1′-cyclopropane]-17-one, for example those prepared and listed in the last paragraph of Example 22, above, yields:

2α-methyl-17α-ethynylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII),
7α-methyl-17α-ethynylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII),
17α-ethynylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
2α-methyl-17α-ethynylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
7α-methyl-17α-ethynylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3β,17β-diol (VIII),
17α-ethynylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
2α-methyl-17α-ethynylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
7α-methyl-17α-ethynylspiro[5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
17α-ethynylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),
2α-methyl-17α-ethynylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI), and
7α-methyl-17α-ethynylspiro[19-nor-5α-androstane-6,1′-cyclopropane]-3β,17β-diol (XXI),

respectively.

Using the procedure of Example 25, but replacing sodium acetylide by sodium methylacetylide or sodium ethylacetylide, there are obtained the corresponding 17α-(1-propynyl) and 17α-(1-butynyl) compounds of Formulae VIII and XXI.

EXAMPLE 26

17β-hydroxy-17α-methyl-spiro[androst-4-ene-6,1′-cyclopropane]-3-one (XIV)

To 300 mg. of 17α - methylspiro[androst - 4 - ene-6,1′-cyclopropane]-3β,17α-diol (XIII) in about 5 ml. of pyridine is added a suspension of chromium trioxide-pyridine complex (prepared from 300 mg. of chromium trioxide and 5 ml. of pyridine). The reaction mixture is allowed to stand at room temperature until the reaction is complete; a period of about 18 to 24 hours is usually sufficient. Water and methylene chloride (1:1) is then added and the mixture is stirred thoroughly. The organic layer is separated, washed with dilute acid, water, dried over anhydrous sodium sulfate and evaporated in vacuo to remove the solvent, giving 17β-hydroxy-17α-methylspiro[androst - 4 - ene-6,1′-cyclopropane]-3-one (XIV), which can be further purified by recrystallization from methylene chloride-Skellysolve B.

In the same manner, substituting as the starting steroid in place of 17α-methylspiro[androst-4-ene-6,1′-cyclopropane]-3β,17β-diol (XIII) in Example 26, other compounds of Formula XIII and the compounds of Formula XXI, for example the 3β-hydroxy-17α-methyl compounds prepared and listed in the last paragraph of Example 24, above, and the 3β-hydroxy-17α-ethynyl compounds prepared in Example 25, above, yields respectively:

17β-hydroxy-2α,17α-dimethylspiro[androst-4-ene-6,1′-cyclopropane]3-one (XIV),
17β-hydroxy-7α,17α-dimethylspiro[androst-4-ene-6,1′-cyclopropane]-3-one (XIV),
17β-hydroxy-17α-methylspiro[19-norandrost-4-ene-6,1′-cyclopropane]-3-one (XIV),

17β-hydroxy-2α,17α-dimethylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-7α,17α-dimethylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-2α,17α-dimethylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-7α,17α-dimethylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-17α-methylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-2α,17α-dimethylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-7α,17α-dimethylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-17α-ethynylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-2α-methyl-17α-ethynylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-7α-methyl-17α-ethynylspiro[androst-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-17α-ethynylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-2α-methyl-17α-ethynylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-6α-methyl-17α-ethynylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one (XIV),
17β-hydroxy-17α-ethynylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-2α-methyl-17α-ethynylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-7α-methyl-17α-ethynylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-17α-ethynylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII),
17β-hydroxy-2α-methyl-17α-ethynylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII), and
17β-hydroxy-7α-methyl-17α-ethynylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one (XXII).

Similarly, the other 3β-hydroxy-17α-lower aliphatic hydrocarbon compounds of Formulae XIII and XXI can be substituted in place of 17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3β,17β-diol, such as the 17α-ethyl, 17α-propyl, 17α-isopropyl, 17α-butyl, 17α-allyl, 17α-vinyl, 17α-propenyl, 17α-isopropenyl, 17α-methallyl, 17α-(1-propynyl), 17α-(1-butynyl), and the like, to obtain the corresponding 3-oxo compounds of Formulae XIV and XXII.

EXAMPLE 27

3β-17β-diacetoxyspiro[androst-4-ene-6,1'-cyclopropane]

Substituting an equivalent amount of 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol (VIII) as the starting steroid in Example 11, above, in place of 17α-methylspiro[androst - 4 - ene - 6,1'-cyclopropane]3β,11β,17β-triol, there is obtained 3β,17β-diacetoxyspiro[androst-4-ene-6,1'-cyclopropane].

In the same manner, other 3β-acylates of 17β-acetoxyspiro[androst-4-ene-6,1'-cyclopropane]-3β-ol can be prepared by substituting in place of acetic anhydride, other acid anhydrides or acid halides of organic carboxylic acids, among which are the hydrocarbon carboxylic acids of from 1 to 16 carbon atoms, inclusive, previously listed.

Similarly, the other compounds of Formula VIII and the compounds of Formulae XVI, XII, XX, XIII and XXI can likewise be converted to their corresponding 3β-acylates. The following conversions are representative:

17β - acetoxyspiro[19 - norandrost-4-ene-6,1'-cyclopropane] - 3β - ol (VIII) with propionic anhydride to obtain 3β - propionyloxy-17β-acetoxyspiro[19-norandrost-4-ene-6,1'-cyclopropane],

17β - acetoxyspiro[5α - androstane-6,1'-cyclopropane]-3β-ol (XVI) with butyric anhydride to obtain 3β-butyryloxy - 17β - acetoxyspiro[5α-androstane-6,1'-cyclopropane],

3β - hydroxyspiro[androst - 4 - ene-6,1'-cyclopropane]-17 - one (XII) with isobutyric anhydride to obtain 3β-isobutyryloxyspiro[androst - 4 - ene-6,1'-cyclopropane]-17-one,

3β - hydroxyspiro[5α-androstane - 6,1'-cyclopropane]-17-one (XX) with hexanoic anhydride to obtain 3β-hexanoyloxyspiro[5α-androstane-6,1'-cyclopropane]-17-one,

17α - methylspiro[androst - 4 - ene-6,1'-cyclopropane]-3β,17β-diol(XIII) with cyclopentylpropionic anhydride to obtain 3β-cyclopentylpropionyloxy-17α-methylspiro[androst - 4 - ene]-17β-ol,

17α - ethynylspiro[5α - androstane-6,1'-cyclopropane]-3β,17β-diol (XXI) with benzoic anhydride to obtain 3β-benzoxy - 17α - ethynylspiro[5α-androstane-6,1'-cyclopropane]-17β-ol,

and the like.

The 3β-acylates of the compounds of Formulae XIII and XXI can be acylated at the 17-position in accordance with the procedure of Example 28, below, to obtain the corresponding 3β,17β-diacylates, wherein the acyl groups present at the 3- and 17-positions can be the same or different.

EXAMPLE 28

17β-propionyloxy-17α-methylspiro[androst-4-ene-6,1'-cyclopropane]-3-one

Substituting an equivalent amount of 17β-hydroxy-17α-methylspiro[androst - 4 - ene - 6,1'-cyclopropane]-3-one (XIV) as the starting steroid in Example 13, above in place of 11β,17β - dihydroxy-17α-methylspiro[androst-4-ene - 6,1' - cyclopropane]-3-one, there is obtained 17β-propionyloxy - 17α - methylspiro[androst - 4 - ene-6,1'-cyclopropane]-3-one.

In the same manner other 17β-acylates of 17β-hydroxy-17α - methylspiro[androst - 4 - ene-6,1'-cyclopropane]-3-one can be prepared by substituting in plate of acetic anhydride, other acid anhydrides or acid halides of organic carboxylic acids, among which are the hydrocarbon carboxylic acids of from 1 to 16 carbon atoms, inclusive, previously listed.

Similarly, the other compounds of Formula XIV and the compounds of Formula XXII can likewise be converted to their corresponding 17β-acylates. The following conversions are representative:

17β - hydroxy - 2α,17α-dimethylspiro[androst-4-ene-6,1'-cyclopropane] - 3 - one (XIV) with acetic anhydride to obtain 17β - acetoxy - 2α,17α-dimethylspiro[androst-4-ene-6,1'-cyclopropane]-3-one,

17β - hydroxy - 7α - methyl-17α-ethynylspiro(androst-4-ene-6,1'-cyclopropane]-3-one (XIV) with succinic anhydride to obtain 17β-hemisuccinoyloxy-7α-methyl-17α-ethynylspiro[androst-4-ene-6,1'-cyclopropane]-3-one,

17β - hydroxy - 17α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane] - 3 - one (XIV) with phenylacetic anhydride to obtain 17β-phenylacetoxy-17α-methylspiro[19-norandrost-4-ene-6,1'-cyclopropane]-3-one,

17β - hydroxy - 17α - methylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII) with acetic anhydride to obtain 17β - acetoxy-17α-methylspiro[5α-androstane-6,1'-cyclopropane]-3-one,

17β - hydroxy - 7α-17α-dimethylspiro[5α-androstane-6,1'-cyclopropane]-3-one (XXII) with butyric anhydride to obtain 17β - butyryloxy - 7α,17α-dimethylspiro[5α-androstane-6,1'-cyclopropane]-3-one,

17β - hydroxy - 17α-ethynylspiro[19-nor-5α-androstane-6,1' - cyclopropane] - 3-one (XXII) with benzoyl chloride to obtain 17β - benzoxy-17α-ethynylspiro[19-nor-5α-androstane-6,1'-cyclopropane]-3-one,

and the like.

Similarly, following the procedure of Example 28 and substituting as starting material therein the 3β,17β-dihydroxy compounds of Formulae XIII and XXI and using

an appropriately larger amount of the selected acid anhydride or acid halide is productive of the corresponding 3β,17β-diacylates thereof. The following conversions are representative:

17α - methylspiro[androst - 4-ene-6,1'-cyclopropane]-3β, 17β-diol (XIII) with propionic anhydride to obtain 3β, 17β - dipropionyloxy - 17α-methylspiro[androst-4-ene-6,1' - cyclopropane],

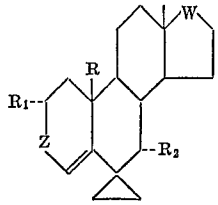
17α - ethynylspiro[5α - androstane - 6,1'-cyclopropane]-3β,17β-diol (XXI) with acetic anhydride to obtain 3β, 17β - diacetoxy - 17α-ethynylspiro[5α-androstane-6,1'-cyclopropane],

and the like.

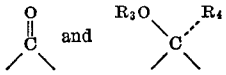
The 3β,17β-diacylates thus obtained can be selectively hydrolyzed at the 3-position using mild hydrolysis conditions in accordance with the procedure of Example 14, above to obtain the corresponding 3β - hydroxy - 17β-acylates.

I claim:

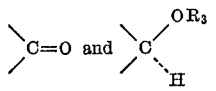
1. A compound of the formula:



wherein R, R_1 R_2 are each selected from the group consisting of hydrogen and methyl; W is selected from the group consisting of



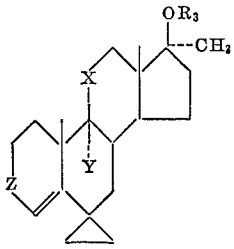
in which R_3 is selected from the group consisting of hydrogen and the acyl radical of a hydrocarbon carboxylic acid of 1 to 16 carbon atoms, inclusive, and R_4 is selected from the group consisting of hydrogen and a lower-aliphatic hydrocarbon radical of 1 to 4 carbon atoms, inclusive; and Z is selected from the group consisting of



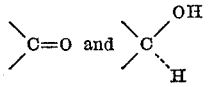
in which R_3 has the meaning given above.

2. 17β - hydroxyspiro[androst - 4 - ene - 6,1'-cyclopropane]-3-one.

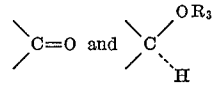
3. A compound of the formula:



wherein R_3 is selected from the group consisting of hydrogen and the acyl radical of a hydrocarbon carboxylic acid of 1 to 16 carbon atoms, inclusive; X is selected from the group consisting of

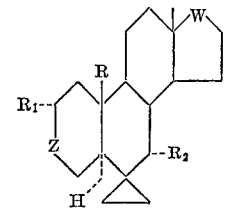


Y is selected from the group consisting of hydrogen and fluorine; and Z is selected from the group consisting of

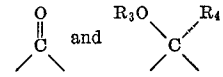


in which R_3 has the meaning given above.

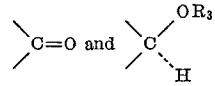
4. A compound of the formula:



wherein R, R_1 and R_2 are each selected from the group consisting of hydrogen and methyl; W is selected from the group consisting of

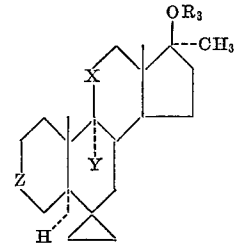


in which R_3 is selected from the group consisting of hydrogen and the acyl radical of a hydrocarbon carboxylic acid of 1 to 16 carbon atoms, inclusive, and R_4 is selected from the group consisting of hydrogen and a lower-aliphatic hydrocarbon radical of 1 to 4 carbon atoms, inclusive; and Z is selected from the group consisting of

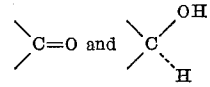


in which R_3 has the meaning given above.

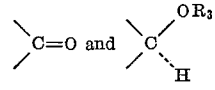
5. A compound of the formula:



wherein R_3 is selected from the group consisting of hydrogen and the acyl radical of a hydrocarbon carboxylic acid of 1 to 16 carbon atoms, inclusive; X is selected from the group consisting of

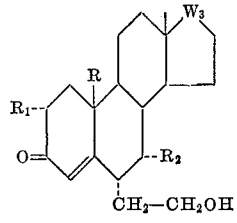


Y is selected from the group consisting of hydrogen and fluorine; and Z is selected from the group consisting of

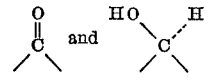


in which R_3 has the meaning given above.

6. A compound of the formula:

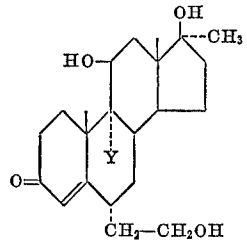


wherein R, R_1 and R_2 are each selected from the group consisting of hydrogen and methyl, and W_3 is selected from the group consisting of



7. 17β - hydroxy - 6α - (2'-hydroxyethyl)-androst-4-ene-3-one.

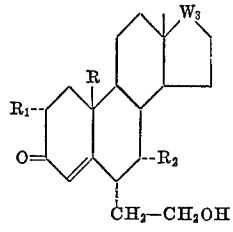
8. A compound of the formula:



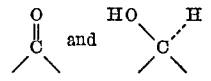
wherein Y is selected from the group consisting of hydrogen and fluorine.

9. The process which comprises treating a 6α-(2'-hydroxyethyl)androst-4-en-3-one with a sulfonic acid halide and subjecting the 6α-(2'-sulfonyloxyethyl)-androst-4-en-3-one so obtained to treatment under basic conditions to produce the corresponding spiro[androst-4-ene-6,1'-cyclopropane]-3-one.

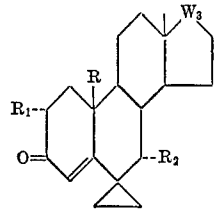
10. The process which comprises treating a 6α-(2'-hydroxyethyl) compound of the formula:



wherein R, R_1 and R_2 are each selected from the group consisting of hydrogen and methyl, and W_3 is selected from the group consisting of



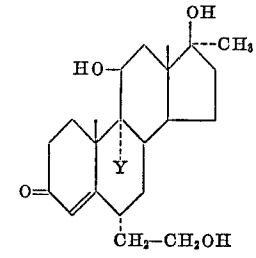
with an organic sulfonic acid halide to produce the corresponding 6α-(2'-organic sulfonyloxyethyl) derivative thereof and subjecting the 6α-(2'-organic sulfonyloxyethyl) derivative so obtained to treatment under basic conditions to produce the corresponding 6,1'-spirocyclopropyl compound of the formula:



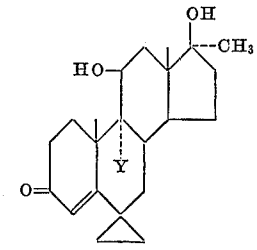
wherein R, R_1, R_2 and W_3 have the meanings given above.

11. The process which comprises treating 17β-hydroxy-6α-(2'-hydroxyethyl)androst-4-en-3-one with p-toluenesulfonyl chloride in the presence of pyridine and subjecting the 17β-hydroxy-6α-(2'-tosyloxyethyl)-androst-4-en-3-one so obtained, to treatment with potassium tert-butoxide to produce 17β-hydroxyspiro[androst-4-ene-6,1'-cyclopropane]-3-one.

12. The process which comprises treating a 6α-(2'-hydroxyethyl) compound of the formula:

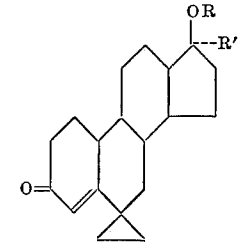


wherein Y is selected from the group consisting of hydrogen and fluorine, with an organic sulfonic acid halide to produce the corresponding 6α-(2'-organic sulfonyloxyethyl)derivative thereof and subjecting the 6α-(2'-organic sulfonyloxyethyl)derivative thus obtained, to treatment under basic conditions to produce the corresponding 6,1'-spirocyclopropyl compound of the formula:



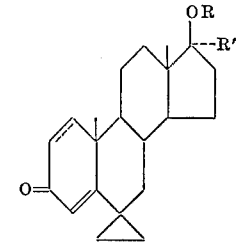
wherein Y has the meaning given above.

13. A compound of the formula



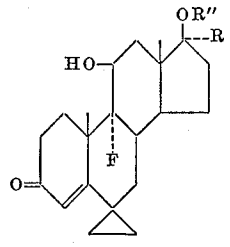
wherein R is selected from the group consisting of hydrogen and the acyl radical of a lower hydrocarbon carboxylic acid and R' is selected from the group consisting of hydrogen, lower alkyl, vinyl and ethynyl.

14. A compound of the formula



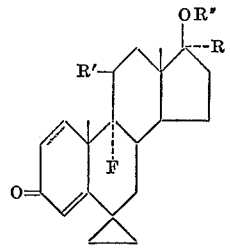
wherein the dotted line between the 1-and 2-positions represents a member selected from the group consisting of a singe bond and a double bond, R is a member selected from the group consisting of hydrogen and the acyl radical of a lower hydrocarbon carboxylic acid and R' is a member selected from the group consisting of hydrogen, a lower saturated aliphatic hydrocarbon radical and a lower unsaturated aliphatic hydrocarbon radical.

15. A compound of the formula



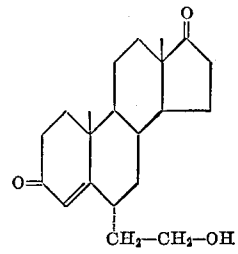
wherein R is selected from the group consisting of H and CH_3: and R'' is selected from the group consisting of H and hydrocarbon acyl.

16. A compound of the formula



wherein the dotted line between the 1- and 2-positions is selected from the group consisting of a single bond and a double bond, R is selected from the group consisting of H and CH_3, R' is selected from the group consisting of β-hydroxy and keto, and R'' is selected from the group consisting of H and hydrocarbon acyl.

17. A compound of the formula



No references cited.

HENRY A. FRENCH, Primary Examiner

U.S. Cl. X.R.

260—239.5, 239.55, 397.3, 397.45, 397.5, 999