A-NOR DERIVATIVES OF THE PREGNANE SERIES AND INTERMEDIATES IN THE PRODUCTION THEREOF

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This invention relates to, and has for its objects, the provision of new physiologically active steroids, methods for preparing the same, and new intermediates useful in said preparation.

The products of this invention can be represented by the formulae:

wherein Z may be hydrogen, hydroxy, halogen (i.e., chloro, fluoro, iso or bromo) or acyloxy; R is hydrogen; R' may be hydrogen or hydroxy; or together R and R' is oxo (O=)

The preferred acyloxy radicals are those of hydrocarbon carboxylic acids of less than twelve carbon atoms, as exemplified by the lower alkanolic acids (e.g., acetic, propionic, butyric, and tert-pentanoic acid), the lower alkanolic acids, the monocyclic aryl carboxylic acids (e.g., benzoic and toluate acid), the monocyclic aryl lower alkanolic acids (e.g., phenacetin and p-phenylpropionic acid), the cycloalkane carboxylic acids and the cycloalkene carboxylic acids.

(In this application and in the appended claims, whenever, in the formulae set forth herein, a curved line (1) is employed in the linkage of atoms, it is meant to denote that the connected atom may be either in the alpha or beta position, as is determined in the respective compounds involved.)

Those final products of this invention which are unsubstituted in the 21-position (i.e., Z is hydrogen or halogen) are physiologically active compounds which possess progestational activity and thus can be employed instead of progesterone, for example, in the treatment of habitual abortion for which purpose they can be administered in the same manner as progesterone, for example, the dosage being adjusted for the relative potency of the particular steroid.

Those final products of this invention which are oxygenated in the 21-position (i.e., Z is hydroxy or acyloxy) are physiologically active compounds which possess mineralocorticoid activity and thus can be employed instead of desoxyxycorticosterone, for example, in the treatment of Addison's disease, for which purpose they can be administered in the same manner as desoxycorticosterone, for example, the dosage being adjusted for the relative potency of the particular steroid.

In addition, it has been found that the compounds of this invention are physiologically active steroids which possess antiandrogenic activity, i.e., they inhibit the action of androgens, and they can be used in the treatment of such conditions as hyperandrogenic acne. The compounds may be formulated for such administration, the concentration and/or dosage being based on the activity of the particular compound and the requirements of the patient.

The final products of this invention are prepared by the process of this invention which entails a number of steps beginning with a triterpenoid acid as a starting material. By a triterpenoid acid, it is here meant a poly-methylsteroid, having a D-ring structure represented by the formula:

wherein R may be the same or different and may be either hydrogen or alkyl and R' may be the same or different and may be selected from the group consisting of hydrogen and hydroxy. Examples of the triterpenoid acids which may be employed in the practice of this invention include eburicoic, polyporic, tumulosic, pinicolic, elemolic, elemonic, dehydroembrusic, dehydroelemolic, dehydroelememonic, and other like acids. The steps of the process (employing eburicoic acid as the starting material) are shown by the following equations wherein R and R' are the same or different and represent hydrogen or acyl, and R'' represents acyl; Z repre-
sents halogen, hydroxy, acyloxy or hydrogen and Y is halide.
In the first step of the process of this invention, eburicolic acid is converted to its 3-ester derivative (Compounds A). The 3-acetate of eburicolic acid is a known compound. Other 3-esters can be prepared in the usual manner by reacting with the desired acylating agent (e.g., acyl chloride or acid anhydride) in the presence of a base, such as pyridine. Although any ester can be prepared, the preferred esters are those with hydrocarbon carboxylic acids of less than twelve carbon atoms. These are formed by reacting with the acyl chloride or acid anhydride of a hydrocarbon carboxylic acid of less than twelve carbon atoms, such as one of the acids listed hereinafter.

The 3-ester is then converted to a corresponding ester of 24-keto-Δ4-lanostene-21-oleic acid (Compounds C). This may be done by ozonolysis of Compounds A and reducing the ozonide formed by treatment with either hydrogen in the presence of a hydrogenation catalyst, such as palladium or charcoal, or an electropositive metal, such as zinc, in the presence of an acid, such as glacial acetic acid, whereby Compounds C are obtained directly. Compounds C can also be obtained in a two-step process by first treating Compounds A with a hydroxylating agent, such as osmium tetroxide, to yield the corresponding 3-ester of 3β,24,28-trihydroxy-Δ4-eburicene-21-oleic acid (Compounds B) and then cleaving the glycol, as by treatment with lead tetracetate to yield Compounds C.

Compounds C are then lactonized by treatment with an acid anhydride and a salt of a strong base and a weak acid, such as sodium acetate in acetic anhydride, to yield a mixture of the α-lactone (Compounds D) and β-lactone (Compounds E) of the corresponding 3-esters of 3β-hydroxy-24-keto-Δ4-lanostene-21-oleic acid. The reaction is preferably carried out at an elevated temperature, such as the reflux temperature of the organic solvent employed and the two lactones are separated chromatographically. However, since both the α-lactone and β-lactone give the same product in the next step of the process of this invention, such separation is not necessary and a mixture of the lactones may be used directly.

Compounds D and E are then dehydrogenated, as by treatment with palladium on charcoal at an elevated temperature, to yield the corresponding 3-ester of 3β,24,28-dihydroxy-Δ4,20(22),23-lanostatriene-21-oleic acid (Compounds F).

Compounds F can then be isomerized to the corresponding 3-acetoxy-24-hydroxy-Δ4,20(22),23-lanostatriene-21-oleic acid derivative (Compounds G), by treatment with hydrogen chloride in a solvent (e.g., glacial acetic acid).

The lanostatriene-21-oleic acid lactones (Compounds F and G) may then be oxidized by treatment with potassium permanganate, and the manganese dioxide reduced by treatment with sulfur dioxide, to form the Δ4,5α-androstene-7,11-dione-17β-carboxylates (Compounds H), which are new compounds of this invention.

Compounds H are then reduced as by treatment with zinc in glacial acetic acid, preferably at elevated temperatures of yield the 5α-androstene-7,11-dione-17β-carboxylates (Compounds J), which are also new compounds of this invention.

Compounds J are then converted to the 11-keto-5α-androstan-17-ol (Compounds K) by treatment first with an alkylidenetriol, such as ethanediol. In the presence of a Lewis acid, such as boron trifluoride etherate, to produce the dithioacrylate ketals (Compounds K). Compounds K may then be treated at elevated temperatures with a sponge nickel catalyst in an organic solvent (e.g., ethanol) to produce Compounds L, which are new compounds of this invention.

Alternatively, Compounds L may be obtained by treating Compounds J with a base (e.g., potassium hydroxide, at elevated temperatures. In addition to the reduction of the 7-keto group, there occurs hydrolysis of the ester groups at C9 and C21, the latter being first by treatment with an acylating agent such as acyl anhydride or acyl chloride, in the presence of a base, such as pyridine, followed by treatment with a methylating agent (e.g., ethereal diazomethane), to produce Compounds L directly.

The 11-keto-5α-androstan-17-ol (Compounds L) may then be dehydrated and rearranged by treatment with phosphorus pentachloride at reduced temperature in the absence of light, to yield the 3-alkylene-11-keto-A-nor-5α-androstan-17-ol (Compounds M), which are also new compounds of this invention.

Compounds M are then treated with ozone and the ozonide formed is reduced, as by treatment with zinc and glacial acetic acid, to yield the 3,11-diketo-A-nor-5α-androstan-17-ol (Compounds N) (wherein R' is 5αH and R is CH3), which are also new compounds of this invention.

These Compounds N (wherein R' is 5αH and R is CH3) may then be hydrolyzed, as by treatment with alkali such as potassium hydroxide at elevated temperatures, to form the free acid compounds with simultaneous epimerization at the C9 position, thus yielding Compounds N (wherein R' is 5βH and R is H), directly. Alternatively, these free acid compounds may be obtained in a stepwise process which entails first, treatment of Compounds N (wherein R' is 5αH and R is CH3) with cold alkali to produce Compounds N (wherein R' is 5βH and R is CH3), followed by treatment with hot alkali to yield Compounds N (wherein R' is 5βH and R is H).

Compounds N may then be treated with an acid halide, for example, oxalyl chloride, to obtain the A-nor-5α-androstane-17β-carboxylic acid halides (Compounds Q), which are also new compounds of the instant invention.

Compounds Q are then treated with a methylating agent, for example, ethereal diazomethane to produce 21-diazoster-20-keto-A-nor-pregnanes (Compounds P) which are new compounds of this invention.

In order to obtain the final products of this invention which are oxygenated in the 21-position (i.e., Z is acetoxy or hydroxy), Compounds P are treated at elevated temperatures with a fatty acid, such as acetic, propionic or butyric acid, to yield the 21-esters of 3,11,20-triketo-A-nor-5α-androstan-17β-carboxylic acid, and these are new compounds of this invention and the other analogs of Compounds Q which are also new compounds of this invention. Alternatively, Compounds Q (wherein Z is acetoxy) may be obtained by first treating Compounds P with a hydroxylactone, such as hydrochloric acid, to yield the 21-halogenated A-nor-pregnanes (Compounds Q), which are also new compounds of this invention, and then acylating the 21-halogenated A-nor-pregnanes as by treatment with potassium acetate and potassium iodide to yield the 21-acetoxy-A-nor-pregnanes (Compounds Q). To obtain the 21-hydroxy A-nor-pregnanes (Compounds Q), the 21-acetoxy compounds are treated with a base, such as potassium carbonate. The 21-hydroxy A-nor-pregnanes (Compounds Q) are also new compounds of this invention.

Compounds Q are then brominated as by treatment with bromine in an acid medium to yield the 21-oxygenated 5-bromo-A-nor-pregnanes (Compounds R), which are also new compounds of this invention. The 21-oxygenated 5-bromo-A-nor-pregnanes (Compounds R) are
then converted to the 21-oxygenated-A-nor-Δ₅-pregnanes (Compounds S) by treatment with a base, such as collidine or lithium halide, e.g., lithium chloride or lithium bromide in dimethylformamide. Compounds S are new final products of this invention.

To obtain the final compounds of this invention, which are not oxygenated in the 21-position (i.e., wherein Z is halide or hydrogen), Compounds P are first treated with a hydrohalide, such as hydroiodic acid, to yield the 21-unsubstituted A-norpregnanes (Compounds Q), which are new compounds of this invention. The 21-unsubstituted pregnanes (Compounds Q) are then brominated, as by treatment with bromine in an acid medium, to yield the 21-unsubstituted 5-bromo-A-norpregnanes (Compounds R), which are then converted to the 21-unsubstituted A-nor-Δ₅-pregnenes (Compounds S) by treatment with a base, such as collidine or a lithium halide, such as lithium chloride, in dimethylformamide. These are also new compounds of the instant invention.

The final products of this invention which are halogenated in the 21-position (i.e., wherein Z may be chlorobromofluoro or iodo) are obtained by first treating, at reduced temperatures, the 21-diazoketone (Compounds P) with a hydrogen halide such as hydrogen chloride, to yield the corresponding 21-halo substituted A-norpregnanes (Compounds Q), which are also new compounds of this invention. The 21-halo substituted compounds are then brominated as by treatment with bromine in an acid medium, and the resultant 5-bromo-21-halo-A-norpregnanes (Compounds R) are dehydrobrominated as by treatment with lithium halide in dimethylformamide to yield the 21-halo-A-nor-Δ₅-pregnenes (Compounds S), which are new final products of the instant invention.

The new final products of this invention may also be obtained by alternate procedures which may be represented by the following equations, wherein R, R', and Z are as hereinbefore defined.

In the first step of the alternate procedure which may be employed to obtain the final products of this invention, the 3,11-diketo-A-norandrostanes (Compounds N) are treated with an enol ester of a carboxylic acid of less than 10 carbon atoms of an aliphatic or alicyclic ketone, such as isopropenyl acetate in the presence of a strong acid, e.g., p-toluenesulfonic acid, to produce the 11-keto-A-nor-Δ₅-androstan-3(11)-ones (Compounds T), which are also new compounds of this invention. Compounds T may then be halogenated, as by treatment with a halogenating agent, such as N-bromosuccinimide, N-bromosuccinimide, dibromomethylhydantoin, bromine, N-chloro-
succhinimid or N-iodoacetylimid, to yield the 5-halo-3,11-diketo-A-nor-5β-androstanones, (Compounds U), which are also new compounds of this invention.

Dehydrohalogenation of Compounds U, as by treatment with lithium bromide in dimethylformamide or collidine, yields a mixture of the unsaturated steroids, A-nor-Δ4-androstanes (Compounds W) and A-nor-Δ5-androstanes (Compounds V), both of which are new compounds of this invention. The mixture of these compounds may be separated into the individual components (Compounds V and Compounds W), by fractional crystallization, in order to further process the individual compounds to obtain the additional products of this invention. In addition to the foregoing, an alternative precedure may be employed to obtain Compounds W, which first entails treating Compounds N with bromine in an acid medium, such as glacial acetic acid, to obtain the 5α-halo-A-nor-5α-androstanes (Compounds Z) which are new compounds of this invention. Compounds Z may then be dehydrohalogenated as by treatment with lithium bromide in dimethylformamide or collidine to yield the A-nor-Δ4-androstan-5-one (Compounds W).

Compound W and V may then be converted to the final A-nor-pregene derivatives of this invention by an identical series of steps. If a compound W is employed, the final product and all the intermediates thereof contain a double bond in the 5,6-position. If a compound V is employed, the final products and all intermediates contain a double bond in the 1,2-position.

In the first of this series of steps, Compounds W and V (R=H) are treated with an acid halide, for example, oxalyl chloride, to obtain the corresponding A-nor-Δ4-androstan-17β-carboxylic acid halides (Compounds AA) and the A-nor-Δ5-androstan-17β-carboxylic acid halides (Compounds DD), respectively. These are the new compounds of this invention. These compounds are then converted to their corresponding diazoketones-A-nor-Δ4-pregenes (Compounds BB) and diazoketones-A-nor-Δ5-pregenes (Compounds EE) derivatives as by treatment with an ethereal solution of diazomethane.

Compounds BB and Compounds EE are then converted to the 21-substituted final products of this invention as set forth hereinafter in the treatment of Compounds P to produce Compounds S and Compounds FF, which are new final products of this invention. Thus, treatment of Compounds EE with a fatty acid, such as acetic, propionic or butyric acid yields the 21-esters of the A-nor-Δ4-pregenes (Compounds FF), which are new final products of this invention. Treating Compounds EE with a hydroxilhalide, such as hydrogen chloride, yields final products of this invention which are 21-halo substituted and are also new final products of this invention. The 21-unsubstituted derivatives are obtained by treating Compounds BB and EE with hydroiodic acid, thus yielding the A-nor-Δ4-pregenes (Compounds S) and the A-nor-Δ5-pregenes (Compounds FF), which are new compounds of the instant invention.

In addition, the 21-unsubstituted, i.e., Z is H, saturated final products of this invention may be obtained by an alternate procedure, which may be represented by the following equations, wherein R, R' and Z are as hereinafter defined:

In the first step of this alternate process, Compounds M (wherein R' is H) are treated with an acid halide, for example, oxalyl chloride, to produce the 3-alkylene-A-nor-5α-androstan-17β-carboxylic acid halides (Compounds CC), which are also new compounds of this invention. Compounds CC are then treated with an ethereal solution of dimethylcadmium to yield the 3-alkylene-A-nor-5α-pregnene-11,20-diketones (Compounds GG) which are also new compounds of this invention. Compounds GG are then ozonized to yield the A-nor-5α-pregnene-3,11,20-triketones (Compounds HH) which are also new compounds of this invention. Compounds HH may then be treated with a base, such as sodium hydroxide to yield the A-nor-5β-pregnene-3,11,20-triketones (Compounds I), wherein Z is H, which are new compounds of this invention.

Additionally, further new products of this invention may be obtained by alternate procedures, employing the same or derivative starting material therefrom. The starting material employed in obtaining the further products of this invention is derived from the triterpenoid acid starting material disclosed hereinafter. The derivative employed in this alternate process is reacted according to the equations set forth below.

The following equations represent additional alternative processes which may be employed in the practice of the invention to yield further new products, wherein R, R' and Z are as hereinafter defined:

In addition to the foregoing, an alternative procedure may be employed to obtain Compounds W, which first entails treating Compounds N with bromine in an acid medium, such as glacial acetic acid, to obtain the 5α-halo-A-nor-5α-androstan-5-one (Compounds Z) which are new compounds of this invention. Compounds Z may then be dehydrohalogenated as by treatment with lithium bromide in dimethylformamide or collidine to yield the A-nor-Δ4-androstan-5-one (Compounds W).
In the first step of this alternate procedure, Compounds J wherein R=CH₃CO and R'=CH₃ are reduced as by the Wolff-Kishner reduction process, employing hydrazine and potassium hydroxide at elevated temperatures to yield the 3-acetoxy-5a-androstan-17β-carboxylate (Compounds JJ) which are new compounds of this invention.

Compounds JJ are then treated in accordance with the procedures set forth hereinabove in the treatment of Compounds L and M to yield the corresponding 3-keto-A-norandrostanes (Compounds KK) which are also new compounds of this invention.

In order to obtain the saturated final products of this alternate procedure (Compounds LL) Compounds KK are treated in exactly the same manner as set forth hereinbefore in the treatment of Compounds N through P to obtain Compounds Q. Thus, Compounds KK (R=H) are treated with an acid halide, converted into the diazoketones as with ethereal diazomethane and then reduced to yield the 3,20-diketo-A-nor-preganes (Compounds LL) which are new compounds of this invention.

Compounds KK may also be treated in accordance with the procedures set forth hereinabove in the treatment of compounds N through BB and EE to yield the saturated A-nor-A₄-pregene-3,20-diones (Compounds MM) and the A-nor-A₆-pregene-3,20-diones (Compounds NN), both of which are new final products of this invention.

Still more new final products of this invention may be obtained by the further processing of some of the derivative material obtained in the treatment of the original triterpenoid acid starting material. The additional processing required to obtain these new final products is set forth.
hydroxy-A-nor-Δ³,5-pregnadienes (Compounds VV) from Compounds QQ. All these compounds are new final products of the instant invention.

In addition to the foregoing, new compounds of this invention may be produced by an alternate procedure. The starting material employed in this alternate process is derived from the treatment of the original triterpenoid acid starting material as described hereinbefore. This alternate process may be represented by the following equations wherein R, R' and Z are as hereinbefore defined:

In the first step of this alternate process, Compounds L, (wherein R is CH₂CO and R' is CH₃) are reduced as by treatment with lithium borohydride to yield the 3-acetoxy-11-hydroxy androstanes (Compounds OO), which are new products of this invention. Compounds OO may then be further treated with a base, such as pyridine, and methane sulfonyl chloride in dimethylformamide to yield the Δ⁹(11)-androsten - 17β-carboxylates (Compounds PP), which are also new compounds of this invention.

Compounds OO and PP may then be treated in accordance with the procedures set forth hereinabove to yield the production of Compounds N from Compounds L and M to yield the corresponding A-nor-Δ³(11)-androstenes (Compounds RR) and 11β-hydroxy-A-norandrostanes (Compounds QQ) which are also new compounds of this invention.

Compounds RR and QQ are then treated in the same manner as set forth hereinabove to yield Compounds Q, S and FF, thus producing respectively, the A-nor-Δ³(11)-pregnenes (Compounds WW), the A-nor-Δ³,8(11)-pregnadienes (Compounds YY), the A-nor-Δ³,5(11)-pregnadienes (Compounds ZZ) and the A-nor-Δ³,5,8-pregnatrienes (Compounds AAA) from Compounds RR; and the 11β-hydroxy-A-nor-pregnanes (Compounds SS), the 11β-hydroxy-A-nor-Δ³-pregnanes (Compounds TT), the 11β-hydroxy-A-nor-Δ³-pregnenes (Compounds UU) and the 11β-
In the first step of this alternate process the A-nor-Δ⁵-androstone - 17β-carboxylates (Compounds V) are ketalized as by treatment with ethylene glycol in an acid medium at elevated temperatures to yield a mixture of the 3-alkyleneoxy-A-nor-Δ⁵-androstenes - 17β-carboxylates (Compounds BBB) and the 3-alkyleneoxy-A-nor-Δ⁵-androstone - 17β-carboxylates (Compounds CCC), which are new compounds of this invention.

The mixture thus obtained may be separated into the individual compounds as by fractional crystallization or chromatographic separation. The 17β-carboxylates (Compounds BBB and CCC) may be converted into the corresponding free acid compounds (wherein R' is H) by treating the 17β-carboxylates with a base, such as potassium hydroxide, in an alcohol medium thus producing the corresponding A-nor-Δ⁵-androstone - 17β-carboxylic acids (Compounds BBB) and the A-nor-Δ⁵-androstone-17β-carboxylic acids (Compounds CCC).

Compounds CCC may then be hydrolyzed by treatment with a mineral acid to yield the free acid of Compounds V. Compounds BBB may be treated with an organic acid, for example acetic acid at room temperature to yield the A-nor-Δ⁵-androstone-3,11-l-diones (Compounds DDD) which are new compounds of this invention. Compounds DDD may then be treated in accordance with the procedures described in the treatment of Compounds N, O and P, in order to yield the final products of this invention, Compounds S. Thus, Compounds DDD are treated with an acid halide to yield Compounds EEE, which are then methylated as with ethereal diazomethane to form Compounds FFF which are then reacted with the appropriate acid to yield the final products of this invention, Compounds S.

Still further processing of some of the derivatives of this invention is possible within the scope thereof. This additional processing may be represented by the following equations, wherein R, R' and Z are as hereinbefore defined:

In the first step of this additional processing Compounds BBB are reduced as by treatment with lithium borohydride, to yield the 3-alkyleneoxy-A-nor-Δ⁵-androsten-11β-ols (Compounds GGG), which are new compounds of this invention. Compounds GGG may then be treated with a base, such as pyridine, and methanesulfonfonyl chloride in dimethylformamide to yield the A-nor-Δ⁵,8(11)-13-androstadienes (Compounds HHH) which are also new compounds of this invention.

Compounds GGG and HHH may then be processed in the same manner to yield the final products of this invention, Compounds TT and Compounds ZZ, respectively. Thus, treatment with an acid halide, e.g., oxalyl chloride yields the corresponding acid chlorides, Compounds JJJ and Compounds KKK; reaction thereof with a methylating agent, e.g., ethereal diazomethane, yields Compounds LLL and MMM, and the reaction of these compounds as set forth hereinabove in the treatment of Compounds BB, yields the final products of this invention, Compounds TT and ZZ, respectively.

AlTERNATIVELY, Compounds GGG and HHH may be hydrolyzed with a fatty acid, such as acetic acid, to yield the Δ⁵-3-keto-A-nor-androstanes (Compounds NNN) and the Δ⁵,8(11)-3-keto-A-nor-androstadienes (Compounds OOO). Compounds NNN and Compounds OOO may then be treated with a mineral acid to yield respectively the Δ⁵,8(11)-3-keto-A-nor-androstanes (Compounds PPP) and the Δ⁵,8(11)-3-keto-A-nor-androstadienes (Compounds QQQ), all of which are new compounds of this invention. Compounds PPP and QQQ may then be treated in accordance with the procedure hereinbefore described.
for the treatment of Compounds N, O and P, is order to yield the final products of this invention, Compounds TT and Compounds ZZ, respectively.

Still more alternate processing of the derivatives of this invention is possible in obtaining the final products thereof. This additional procedure is represented by the following equations wherein R, R' and Z are as hereinbefore defined:

The first step of this alternate process involves ketalizing Compounds N by treatment with ethylene glycol in an acid medium at elevated temperatures to yield the 3-alkylenedioxy-A-norandrostanes (Compounds RRR) which are new compounds of this invention. Compounds RRR are then reduced as by treatment with lithium borohydride to yield the 3-alkylenedioxy-1,4-alkylenedioxy-A-norandrostanes (Compounds SSS), which are also new compounds of this invention. Compounds SSS may then be treated with a base, such as pyridine, and methanesulfonyl chloride, in dimethylformamide to yield the A-nor-Δ²(14)-androstenes (Compounds TTT), which are also new compounds of this invention. Compounds TTT and SSS may then be treated in the same manner to yield the final products of this invention Compounds WW and SS, respectively. Thus, treatment of the compounds with an
acid halide, e.g., oxalyl chloride yields the corresponding acid chlorides, Compounds VVV and UUU; reaction thereof with a methylating agent, e.g., ethereal diazomethane, yields Compounds XXX and WWW; and the treatment of these compounds as set forth hereinafter in the treatment of Compounds BB, yields the final products of this invention, Compounds WW and SS respectively.

In all the alternate process of this invention wherein the intermediate compounds employed in the production of the final products, possess a double bond in the six position it has been found that the final products will always possess a double bond in the five position. This shift in the bond position occurs whenever a mineral acid is employed in the process. To date it has not been found possible in the practice of this invention to obtain the final products of the invention possessing a double bond in the six position.

The following examples illustrate the invention (all temperatures being in centigrade):

**EXAMPLE 1**

**Eburicic acid 3-propionate (II)**

To a solution of 10 g. of eburicic acid in 50 ml. of anhydrous pyridine is added 10 ml. of propionic anhydride and the mixture is allowed to remain at room temperature for 18 hours. Five grams of ice is then added and 30 minutes later the mixture is diluted slowly with 250 ml. of ice and water. The resulting precipitate is filtered, washed thoroughly with water, dried in vacuo and recrystallized from 95% alcohol yielding pure eburicic acid 3-propionate (II).

Similarly, by substituting other acid anhydrides of acyl halides for the propionic anhydride in the procedure of Example 1, the corresponding 3-esters are formed. Thus, butyric anhydride and benzoyl chloride yield the 3-butyrate and 3-benzoate of eburic acid, respectively.

**EXAMPLE 2**

**3β-acetoxy-24-keto-Δ5-lanostene-21-oic acid (IV)**

Through a solution of 15 g. of eburicic acid 3-acetate (I) in a mixture of 150 ml. of chloroform and 150 ml. of ethyl acetate, cooled in a Dry Ice-acetone bath, is passed 26.2 l. of ozone (1 mole of ozone contained in 89 l. of oxygen). The resulting solution is allowed to warm to room temperature and then added to a suspension of 975 mg. of pre-reduced 5% palladium on charcoal catalyst in 50 ml. of ethyl acetate. 550 ml. of hydrogen is taken up rapidly, following which the solution is filtered and the filtrate evaporated to dryness in vacuo.

Alternately the ozonide can be decomposed with zinc in acetic acid as follows: The ozonolysis mixture obtained from 50 g. of eburic acid 3-acetate in 50 ml. of chloroform and 500 ml. of ethyl acetate, is allowed to warm up to --10° when it is diluted with 50 ml. of glacial acetic acid. Powdered zinc is then added in portions with stirring and the temperature allowed to rise to -4-5°. A total of 25 g. of zinc is required. After 2½ hours the reaction mixture is filtered and the zinc and zinc salts washed thoroughly with ethyl acetate. The ethyl acetate-chloroform filtrate is washed thoroughly with water, dried over sodium sulfate and evaporated to dryness in vacuo. A total of about 56 g. of the crude keto acid IV is obtained.

The acid (IV) is obtained in pure form by chromatography on neutral alumina. For this purpose a solution of 14 g. of the crude acid is dissolved in 50 ml. of benzene and poured to the column containing 50% chloroform benzene (9:l.) elutes about 1.9 g. of pure acid melting at about 234-236°, which is followed by about 1.2 g. of acid when the eluant is changed to 75% chloroform in benzene (3:1). An additional 1.3 g. of pure acid is obtained with chloroform (5:1). The column is then stripped with 5% acetic acid in chloroform (2 L) which elutes about 10.4 g. of crude material which is dissolved in 100 ml. of benzene and chromatographed on 200 g. of silica gel. Elution with benzene (750 ml.) gives about 4 g. of amorphous solids (XXX) which is followed by crystalline acid (about 2.4 g.) when the eluant is changed to chloroform (8:1). The pure acid (IV) has the following properties: M.P. 236-238°; [α]D = +52°(c. 49 in chlf.;

\[\text{C}_{24}^\text{max} \times \text{max} = 5.78 \text{ and } 5.96 \mu; \text{C}_{24}^\text{dim} = 5.83-5.90; 8.05; 9.76 \text{ and 9.94} \mu\]

**Analysis.**-Calcd. for C_{24}H_{40}O_5: C, 74.67; H, 9.79. Found: C, 74.64; H, 9.54.

**EXAMPLE 3**

3β-acetony-24,28-dihydroxy-Δ5-eburicene-21-oic acid (III)

To a solution of 2 g. of eburic acid 3-acetate (I) in 20 ml. of benzene and 2 ml. of pyridine is added dropwise a solution of 1 g. of osmium tetroxide in 10 ml. of benzene. Addition is complete in 1 hour and the reaction mixture is allowed to remain at room temperature for an additional 4 hours. The resulting dark solid solution is filtered through 76 ml. of dioxane and saturated with hydrogen sulfide for 15 minutes. The resulting suspension is filtered and the precipitated salt is washed thoroughly with water, dried in vacuo and recrystallized from 95% alcohol yielding pure eburic acid 3-propionate (II).

Similarly, by substituting other acids anhydrides of acyl halides for the propionic anhydride in the procedure of Example 1, the corresponding 3-esters are formed. Thus, butyric anhydride and benzoyl chloride yield the 3-butyrate and 3-benzoate of eburic acid, respectively.

**EXAMPLE 4**

3β-acetoxy-24-keto-Δ5-lanostene-21-oic acid (IV)

A solution of 1.17 g. of the 24,28-dihydroxy acid (III) in 200 ml. of 0.108 molar lead tetraacetate solution in glacial acetic acid is allowed to stand at room temperature for 35 minutes. A few drops of ethylene glycol are then added to reduce the excess lead tetraacetate and the solution is concentrated in vacuo and diluted with water. The resulting suspension is extracted with ethyl acetate and the ethyl acetate extract washed several times with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude residue (about 1.07 g.) on recrystallization from acetonitrile furnishes about 700 mg. of the pure keto acid IV possessing the following properties: M.P. about 225-227°; [α]D = +50° (c. 43 in chlf.;

**Analysis.**-Calcd. for C_{24}H_{40}O_5: C, 74.67; H, 9.79. Found: C, 74.32; H, 9.50.

This acid is identical in all respects with the product obtained in Example 2.

**EXAMPLE 5**

3β-acetoxy-24-hydroxy-Δ5-21-lanostadiene-21-oic acid lactone (α-lactone) (V) and 3β-acetoxy-24-hydroxy-Δ5-21-lanostadiene-21-oic acid lactone (β-lactone) (VI)

To a solution of 15.4 g. of 3β-acetoxy-24-keto-Δ5-lanostene-21-oic acid (IV) in 150 ml. of anhydrous acid is added 3.75 g. of anhydrous sodium acetate and the resulting suspension is heated under reflux for 10 hours. Upon cooling, the acylic anhydride solution is decanted from the sodium acetate and the latter washed thoroughly with benzene. The combined acylic anhydride-benzene solutions are evaporated to dryness in vacuo, the residue redissolved in benzene and filtered from the precipitated sodium acetate. The clear benzene solution is evaporated to dryness leaving a mixture of the α- and β-enol lactones (V and VI) (about 15.1 g.). Separation is achieved by chromatography on neutral alumina as follows: The total residue is dissolved in 50 ml. of benzene and 50 ml. of hexane and charged to a column containing 300 g. of
neutral alumina. Elution with 250 ml of benzene-hexane (1:1) produces about 3.1 g of crude crystalline 3β-acetoxy-24-hydroxy-Δ₂₀₂₄₁₀-lanostadiene-21-oic acid lactone (α-lactone) (V), which after crystallization from 95% ethanol is analytically pure and has the following properties: M.P. about 169-171°; $[\alpha]_D^{20} +37$°; $\lambda_{\text{max}}$ 5.69, 5.78, 5.93 (weak), 8.05, 12.05, 12.62 and 13.30 μ.

The 12.05 and 12.63 μ bands are diagnostic for the α-lactone and are absent in the β-lactone.


Continued elution of the alumina column with benzene (8 L) produces a total of about 4 g of material in 12 fractions, all of which melt between 150-160° and represent a mixture of the α- and β-lactones. Rechromatography of this mixture is necessary to obtain the pure β-lactone. For the purpose all of the fractions are combined (4 g), dissolved in 20 ml of benzene and 80 ml of hexane and charged to a column of 120 g of neutral alumina. Elution with benzene-hexane (1:1) produces in the first 500 ml, about 827 mg of the pure α-lactone (V) which is followed by elution with the same solvent mixture (5:5:1) and on elution with benzene-hexane (1:1:2:1) by a total of about 2.9 g of material, representing a mixture of α- and β-lactone melting at about 158-160°. Continued elution of the column with benzene (9 L) yields a total of about 1.2 g of material which after recrystallization ethanol constitutes pure 3β-acetoxy-24-hydroxy-Δ₅₁₀-lanostadiene-21-oic acid lactone (β-lactone) (VI) (about 404 mg) possessing the following properties: M.P. about 190-191°; $[\alpha]_D^{20} +64$° (c, .87 in chlfd.).

$\lambda_{\text{max}}$ 5.70, 5.79, 5.97 (weak), 8.08, 11.50, 11.50, 11.80, and 13.50 μ.

The μ band is absent in the α-lactone.

**Analysis.**—Calcd. for C₃₅H₅₇O₄: C, 77.37; H, 9.73. Found: C, 77.56; H, 9.73.

**EXAMPLE 6**

3β-acetoxy-24-hydroxy-Δ₅₁₀₂₄₁₀-lanostadiene-21-oic acid lactone (α-pyrones) (VII)

A suspension of 180 mg of 10% palladium on charcoal in 25 ml of p-cymene is distilled until approximately 3 ml of solvent have been removed. The final temperature of the vapors is over 170°. 250 ml of the thoroughly dried α-enol lactone (V) is then added and the resulting suspension heated under reflux with stirring for 2 hours under a blanket of nitrogen. The mixture is cooled, filtered and the solvent removed in vacuo. The residual crystalline material on recrystallization from absolute ethanol furnishes the pure α-pyrone (VI) in about 75% yield possessing the following properties: M.P. about 228-228.5°; $[\alpha]_D^{20} -114$° (chlfd.).

$\lambda_{\text{max}}$ 305 μ (e=5,850); $\lambda_{\text{max}}$ 5.79, 5.90, 6.11, 6.35, 8.95, 11.90 and 12.69 μ.


When the β-enol lactone (VI) is substituted for the α-lactone (V) in Example 6 and the reaction time is prolonged to 6 hours, the pyrone (VII) is obtained in about 60% yield. Moreover, when a mixture of α- and β-enol lactones (V and VI) (80 g) is dehydrogenated with 80 g of 10% palladium on charcoal in 700 ml of p-cymene for 6 hours, about 50 g of the pure α-pyrone (VII) of M.P. about 226-228° is obtained.

Furthermore, if another ester of euricolic acid, such as the 3-propionate (II), the 3-butyrate or the 3-benzoate is substituted for the 3-acetate in the procedures of either Example 2 or Example 3 and the procedures of Examples 2 through 6 are carried out, the corresponding 3-esters are obtained.

**EXAMPLE 7**

3β,24-dihydroxy-Δ₂₀₂₄₁₀-lanostaterene-21-oic acid lactone (VIII)

To a solution of 510 mg of potassium hydroxide in 10 ml of ethylene glycol is added 73 mg of the finely ground α-pyrene acetate (VII). The suspension is stirred and immersed in an oil bath held at a temperature of 150°. After 5 minutes there results a clear pale yellow solution which is heated for an additional 4 minutes and then cooled. 25 ml of water is added and the mixture extracted with ether. The ether extract is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness in vacuo. About 60 mg of crystalline residue is obtained which on recrystallization from acetone furnishes long needles of the α-pyrene 3-ol (VIII) possessing the following properties: M.P. about 254-255°;

$\lambda_{\text{max}}$ 503 μ (e=0.060); $\lambda_{\text{max}}$ 2.74, 2.86, 5.87, 6.09, 6.35, 11.86 and 12.62 μ.


**EXAMPLE 8**

24-hydroxy-3-keto-Δ₂₀₂₄₁₀-lanostaterene-21-oic acid lactone

To a solution of 95 mg of 3β,24-dihydroxy-Δ₂₀₂₄₁₀-lanostaterene-21-oic acid lactone (VIII) in 3 ml of acetone is added 1 ml of a 90% aqueous acetone solution of 20 mg of chromium trioxide and 32 mg of concentrated sulfuric acid. After 10 minutes methanol is added to reduce excess chromium trioxide and the solution is diluted with water and extracted with chloroform. The chloroform extract is dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline residue on recrystallization from acetone/nitrite produces the analytically pure 3-ketone possessing the following properties: M.P. about 230-232°;

$\lambda_{\text{max}}$ 5.87, 6.08, 6.30, 12.02 and 12.63 μ.


**EXAMPLE 9**

3β-acetoxy-24-hydroxy-Δ₅₁₀₂₄₁₀-lanostaterene-21-oic acid lactone (IX)

A solution of 5 g. of 3β-acetoxy-24-hydroxy-Δ₅₁₀₂₄₁₀-lanostaterene-21-oic acid lactone (VII) in 350 ml of glacial acetic acid is saturated with dry hydrogen chloride gas first at 10° and finally as more HCl dissolves at 0°. This requires a total of 30 minutes. The solution is maintained for an additional hour at 0° and then evaporated to dryness in vacuo. The resulting crystalline residue on recrystallization from 95% ethanol and chloroform furnishes about 3.75 g (75%) of a mixture consisting largely of the Δ- and some of the Δ-isomer, M.P. 229-231°; $[\alpha]_D^{20} -135$° (chlfd.). A sample of this product is chromatographed on acid-washed alumina using a 100:1 ratio of alumina to sample. After elution of the Δ-isomer with chloroform-benzene (1:8) the main fraction is eluted with pure chloroform to give the pure Δ-isomer (IX), which on recrystallization from methanol has the following properties: M.P. 230-230.5°; $[\alpha]_D^{20} -144$° (chlfd.).


$\lambda_{\text{max}}$ essentially identical with the Δ-isomer VII except for the presence of a medium band at 12.05 μ, which is weak in the latter.
EXAMPLE 10

3β-hydroxy-24-keto-Δ7α(25,28),21-lanostatriene-21-oic acid lactone (X)

Following the procedure of Example 9 but substituting 5 g. of 3β-hydroxy-24-keto-Δ7α(25,28),21-lanostatriene-21-oic acid lactone (VIII) for the acetate (VII), 3β-hydroxy-24-keto-Δ7α(25,28),21-lanostatriene-21-oic acid lactone (X) is obtained.

EXAMPLE 11

3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-one-17β-carboxylic acid (XI)

To a solution of 50 g. of 3β-acetoxy-24-hydroxy-Δ7α(25,28),21-lanostatriene-21-oic acid 21,24-lactone (VII) in 3 l. of acetone maintained at a temperature of 33-37° is stirred with a solution of 120 g. of finely pulverized potassium permanganate. The potassium permanganate is added in 20 g. portions, first more rapidly, later on at greater intervals so as to maintain the proper temperature and making sure that the permanganate color is discharged prior to new additions. The total time of addition is about 1 hour and 20 minutes and the reaction is allowed to proceed until all the permanganate color is discharged (approximately an additional 1 to 1½ hours). Upon completion of the oxidation 60 ml. of water is added, the mixture cooled to 0° in an ice-bath and sulfur dioxide is passed through the solution until all the manganese dioxide has been transformed into colorless manganese sulfate. The suspension is filtered and the filter cake washed thoroughly with hot acetone. The yellow acetonc solution is concentrated in vacuo to 800 ml. and the 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) precipitated by the addition with stirring of 2 l. of ice and water. The precipitated acid (XI) is filtered off, washed with water and dried in vacuo to 40°. The dried material (30.8 g.) is dissolved in 200 ml. of hot absolute alcohol and allowed to crystallize. 2.3 g. of lactone starting material (VII) separates and the resulting mother liquor is taken to dryness. The residue is then dissolved in 75 ml. of acetone and the acid (XI) allowed to crystallize. The first crop of 12.3 g. of 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) melts at 245-248°, the second crop of 1.61 g. of 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) melts at 242-245° and the third crop of 2.17 g. of 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) melts at 235-238°. The analytically pure 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) obtained by recrystallization from methanol has the following properties: M. P. 252-255°; [α]D25 +85° (c. 1.24 in chlor.).

Analysis (after drying at 135°).—Calcd. for C24H34O2 .H2O

(439.53): C, 68.31; H, 8.02. Found: C, 68.51; H, 7.95.

EXAMPLE 12

3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI)

Following the procedure set forth in Example 11 but substituting 50 g. of 3β-acetoxy-24-hydroxy-Δ7α(25,28),21-lanostatriene-21-oic acid 21,24-lactone (IX) for 3β-acetoxy-24-hydroxy-Δ7α(25,28),21-lanostatriene-21-oic acid 21,24-lactone (IX) for 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI), yields 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI).

EXAMPLE 13

Methyl 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylate (XII)

To a suspension of 12.5 g. of 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylic acid (XI) in 250 ml. of methanol is added at 0° a solution of diazomethane in ether there is no longer an evolution of nitrogen. Upon completion of the reaction the ether is removed in vacuo and the solution concentrated to a total volume of about 75 ml. The methyl 3β-acetoxy-4,4,14-trimethyl-Δ5α-androstene-7,11-dione-17β-carboxylate (XII) readily crystallizes yielding 9.2 g. of material (M. P. 170-172°) in the first crop and an additional 2 g. (M. P. 158-160°) in the second crop. The analytical sample, recrystallized from methanol, has the following properties: M. P. 178-179°; [α]D25 +88° (c. 1.18 in chlor.).

λmax 268 mμ (ε=8,400); λ224 5.73, 5.80 and 5.94 μμ.

Analysis.—Calcd. for C27H38O3 (444.55): C, 70.24; H, 8.16; OCH2= 6.98. Found: C, 70.36; H, 8.11; OCH2= 6.89.

EXAMPLE 14

Methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-dione-17β-carboxylate (XVII)

To a refluxing solution of 17 g. of methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-dione-17β-carboxylate (XII) in 425 ml. of glacial acetic acid is added, over a 20 minute period, 170 g. of 20 mesh granular zinc. The yellow color lightens and complete decolorization is achieved by the portionwise addition of a total of 3 g. of zinc dust. Total reaction time is 2 hours. The solution is cooled and filtered, the zinc washed with chloroform and the solvents concentrated to small volume in vacuo. The residue is distributed between water and chloroform, the chloroform solution washed with dilute sodium bicarbonate, dried over sodium sulfate and concentrated to a small volume. Upon addition of methanol the very insoluble methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-dione-17β-carboxylate (XVII) crystallizes rapidly, yielding a first crop of 12.5 of XVII having an M. P. of 258-260° and a second crop of 2.7 g. of XVII having an M. P. of 235-240°. The analytically pure compound is obtained by recrystallization from chloroform-methanol or acetonitrile and has the following properties: M. P. 262°.

λmax 268 mμ, no absorption at 280 mμ; λ224 5.73, 5.85, 8.00 and 8.33 μμ; [α]D25 +70° (c. 1.00 in chlor.).

Analysis.—Calcd. for C27H38O3 (446.56): C, 69.93; H, 8.38. Found: C, 70.07; H, 8.38.

EXAMPLE 15

Methyl 3β-acetoxy-7-ethylenediothio-4,4,14-trimethyl-5α-androstene-11-one-17β-carboxylate (XVIII)

To a mixture of 38 ml. of ethanethiol and 47 ml. of twice distilled boron trifluoride etherate is added 14 g. of methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-dione-17β-carboxylate (XV). All the material dissolves within 1.5 hours and after a total reaction time of 23 hours at room temperature, 290 ml. of cold methanol is added. The mixture is chilled in an ice-bath for 1 hour and filtered. The crystals are washed thoroughly with cold methanol and dried in a vacuum oven at 40°. 12.5 g. of methyl 3β-acetoxy-7-ethylenediothio-4,4,14-trimethyl-5α-androstene-11-one-17β-carboxylate (XVIII) melting at 210-211° is obtained. The analytical sample, recrystallized from methanol and chloroform, has the following properties: M. P. 211-212°; [α]D25 +19° (c. 0.10 in chlor.).

λmax 5.77, 5.83, 8.00 and 8.33 μμ.

Analysis.—Calcd. for C27H38O3S2 (522.73): C, 64.32; H, 8.09; S, 12.27. Found: C, 64.12; H, 8.11; S, 12.14.
EXAMPLE 16

Methyl 3α-acetoxy-4,4,14-trimethyl-5α-androstene-11-one-17β-carboxylate (XIX)

To a solution of 12.3 g. of methyl 3α-acetoxy-7-ethylene-1,4,4,14 - trimethyl-5α-androstane-11-one-17β-carboxylate (XVIII) in 1.2 l. of absolute ethanol is added 414 ml. of commercial Raney nickel, from which all water had been removed by repeated washing with absolute ethanol. The resulting suspension is refluxed for 16 hours, the reaction mixture filtered while hot and the Raney nickel cake washed with large volumes of hot ethanol taking care to keep the pyrophoric catalyst covered with solvent at all times. The filtrate and washings are concentrated until crystals appear. These crystals are filtered after cooling yielding a first crop of 8.5 g. of (XIX) melting at 218°-220° and a second crop of 508 mg. of (XIX) melting at 217°-219°. The analytically pure material obtained by recrystallization from methanol has the following properties: M.P. 219°-220°; \( \lambda_{D}^\text{max} 5.78, 5.82, 8.01 \text{ and } 8.36 \mu \) (c. 61 in clff).

Analysis.—Calcd. for C_{32}H_{44}O_{5} (431.58): C, 71.19; H, 9.32. Found: C, 72.54; H, 9.39.

EXAMPLE 17

4,4,14-trimethyl-5α-androstane-3β-ol-11-one-17β-carboxylic acid (XX)

A solution of 4 g. of methyl 3α-acetoxy-4,4,14-trimethyl-5α-androstane-11-one-17β-carboxylate (XIX) in 600 ml. of 5% methanolic KOH (7.3 N) and 40 ml. of water is refluxed under nitrogen for 71/2 hours. The solution is acidified with glacial acetic acid and the resulting solution concentrated in vacuo. Water is added and after cooling the resulting crystals removed by filtration. After drying, 3.45 g. of the acid (XX), melting at 310°, is obtained. The analytically pure material, crystallized from chloroform-methanol, has the following properties: M.P. 355°-354°; \( \lambda_{D}^\text{max} 2.84, 5.77 \text{ and } 5.92 \mu \) (c. 47 in methanol).

Analysis.—Calcd. for C_{32}H_{44}O_{5} (376.52): C, 73.36; H, 9.64. Found: C, 73.43; H, 9.40.

EXAMPLE 18

4,4,14-trimethyl-5α-androstene-3β-ol-7,11-diene-17β-carboxylic acid (XXIII)

Following the procedure set forth in Example 17 but substituting 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-diene-17β-carboxylic acid (XI) for methyl 3α-acetoxy - 4,4,14 - trimethyl-5α-androstane-11-one-17β-carboxylate (XIX) yields 4,4,14-trimethyl-5α-androstene-3β-ol-7,11-diene-17β-carboxylic acid (XXIII).

Similarly, following the procedure set forth in Example 17, but substituting methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstene-7,11-diene-17β-carboxylate (XXII) for methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstane-11-one-17β-carboxylate (XIX), yields 4,4,14-trimethyl-5α-androstene-3β-ol-7,11-diene-17β-carboxylic acid (XIII).

EXAMPLE 19

4,4,14-trimethyl-5α-androstene-3β-ol-7,11-diene-17β-carboxylic acid (XVI)

Following the procedure set forth in Example 17 but substituting methyl 3β-acetoxy-4,4,14-trimethyl-5α-androstane-7,11-diene-17β-carboxylate (XV) for methyl 3β-acetoxy - 4,4,14 - trimethyl-5α-androstane-11-one-17β-carboxylate (XIX), yields 4,4,14-trimethyl-5α-androstene-3β-ol-7,11-diene-17β-carboxylic acid (XVI).

EXAMPLE 20

Methyl 4,4,14-trimethyl-5α-androstane-3β-ol-11-one-17β-carboxylate (XXI)

To a suspension of 2 g. of 4,4,14-trimethyl-5α-androstane-3β-ol-11-one-17β-carboxylic acid (XX) in 40 ml. of methanol is added, at 0°, an excess of diazomethane in ether. After 20 minutes the excess diazomethane is removed by the addition of glacial acetic acid and the ether-methanol solution concentrated in vacuo. From the concentrated methanolic solution 1.9 g. of methyl 4,4,14 - trimethyl - 5α - androstane - 3β - ol - 11-one-17β-carboxylate (XXI) is readily crystallized having an M.P. 238°-239°. Analytically pure material is obtained by recrystallization from methanol and possesses the following properties: M.P. 240°-241°; \( \lambda_{D}^\text{max} +60° \) (c., 1.08 in clff.).

Analysis.—Calcd. for C_{39}H_{48}O_{4} (390): C, 73.80; H, 8.91. Found: C, 73.81; H, 9.61.

EXAMPLE 21

Methyl 4,4,14-trimethyl-5α-androstane-3β-ol-7,11-diene-17β-carboxylate (XIV)

Following the procedure set forth in Example 20, but substituting 4,4,14-trimethyl-5α-androstane-3β-ol-7,11-diene-17β-carboxylic acid (XIII) for 4,4,14-trimethyl-5α-androstane-3β-ol-11-one-17β-carboxylic acid (XX), yields methyl - 4,4,14 - trimethyl - 5α - androstane - 3β - ol - 7,11-diene-17β-carboxylate (XIV).

EXAMPLE 22

Methyl 4,4,14-trimethyl-5α-androstane-3β-ol-7,11-diene-17β-carboxylate (XVII)

Following the procedure set forth in Example 20, but substituting 4,4,14-trimethyl-5α-androstane-3β-ol-7,11-diene-17β-carboxylic acid (XVI) for 4,4,14-trimethyl-5α-androstane-3β-ol-11-one-17β-carboxylic acid (XX) yields methyl - 4,4,14 - trimethyl - 5α - androstane - 3β - ol - 7,11-diene-17β-carboxylate (XVII).

EXAMPLE 23

Methyl 4,4,14-trimethyl-3α-acetoxy-5α-androstane-11β-ol-17β-carboxylate (LXXXVI)

A solution of 500 mg. of methyl 4,4,14-trimethyl-3β-acetoxy-5α-androstane-11β-ol-17β-carboxylate (XIX) and 500 mg. of lithium borohydride in 50 ml. of freshly distilled tetrahydrofuran is stirred at room temperature for 2 hours. Excess lithium borohydride is then destroyed with 10% aqueous acetic acid, the mixture diluted with water and chloroform and the chloroform extract washed with water, dilute bicarbonate and again with water. After drying over sodium sulfate the solvents are removed in vacuo and the resulting residue recrystallized from methanol. The analytical sample has the following properties: M.P. 219°-220°; \( \lambda_{D}^\text{max} +72° \) (c., 1.04 in clff.).

Analysis.—Calcd. for C_{32}H_{44}O_{5} (534.60): C, 71.85; H, 9.74. Found C, 71.94; H, 9.76.

EXAMPLE 24

Methyl 4,4,14-trimethyl-3β-acetoxy-5α-androstene-17β-carboxylate (LXXXVII)

A solution of 250 mg. of methyl 4,4,14-trimethyl-3β-acetoxy-5α-androstene-11β-ol-17β-carboxylate (XIX) in 10 ml. of dimethylformamide, 1 ml. of anhydrous pyridine and .5 ml. of methanesulfonic chloride is allowed to remain at room temperature for 17 hours. Water is added to the mixture and, after cooling, the crystals are removed by filtration. The washed and dried crystals weigh 207 mg. and melt at 163°-164°. Recrystallization
of this material from methanol furnishes the analytically pure compound melting at 167°; \( \alpha_d^25 \pm 95^\circ \) (c., 3 in chl)

\[ \lambda_{\text{max}} = 5.75, 8.02 \text{ and } 8.36 \mu \]

Analysis.—Calcd. for C$_2$H$_4$O$_4$ (416.98): C, 74.96; H, 9.60. Found: C, 74.75; H, 9.82.

**EXAMPLE 25**

**Methyl 6,4,14-trimethyl-3β-acetoxy-5α-androstan-17β-carboxylate (LXVI)**

A solution of 200 mg. of methyl-6,4,14-trimethyl-3β-acetoxy-5α-androstan-7,11-dione-17β-carboxylate (XV), 200 mg. of hydrazine hydrate and 500 mg. of potassium hydroxide in 5 ml. of ethylene glycol is refluxed for 24 hours. The mixture is then cooled, diluted with water, acidified to pH 2 and the steroids extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and the solvent removed in vacuo. The resulting material is recrystallized with 5% cc. of acetic anhydride and 5% cc. of pyridine for 18 hours at room temperature and the resulting material remelted with diazomethane. Removal of the solvent leaves the methyl 6,4,14-trimethyl-3β-acetoxy-5α-androstan-17β-carboxylate as a crystalline solid.

Similarly, following the procedure set forth in Example 25, but substituting methyl-6,4,14-trimethyl-3β-acetoxy-5α-androstan-7,11-dione-17β-carboxylate (XXV) for methyl-6,4,14-trimethyl-3β-acetoxy-5α-androstan-7,11-dione-17β-carboxylate (XV), methyl-6,4,14-trimethyl-3β-acetoxy-5α-androstan-17β-carboxylate (LXVI) is obtained.

**EXAMPLE 26**

**Methyl 3-isopropylidene-14-methyl-A-nor-5α-androstan-11-one-17β-carboxylate (XXII)**

To a solution of 1.2 g. of methyl-6,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylate (XXI) in 240 ml. of dry toluene maintained at 0° and protected from light, is added 1.2 g. of phosphorus pentachloride. Immediately after the addition of the latter a rapid stream of helium gas is passed through the suspension with stirring. After 20 minutes saturated sodium bicarbonate is added and the two layers mixed thoroughly until all the phosphorus oxychloride is hydrolyzed. The toluene solution is washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The residue upon crystallization from methanol has the following properties: M.P. 150-151°; \( \alpha_d^{59} \pm 63^\circ \) (c., 0.59 in chl)

\[ \lambda_{\text{max}} = 5.72, 5.84 \mu \]


**EXAMPLE 27**

**4,4,14-trimethyl-5α-androstan-3β-11β-diol-17β-carboxylic acid**

Following the procedure set forth in Example 17 but substituting methyl-6,4,14-trimethyl-3β-acetoxy-5α-androstan-11β-ol-17β-carboxylate for methyl-3β-acetoxy-4,4,14-trimethyl-5α-androstan-11-one-17β-carboxylate (XIX), yields 4,4,14-trimethyl-5α-androstan-3β-11β-diol-17β-carboxylic acid (XXII).

**EXAMPLE 28**

**Methyl 4,4,14-trimethyl-5α-androstan-3β-11β-diol-17β-carboxylate**

Following the procedure set forth in Example 20, but substituting 4,4,14-trimethyl-5α-androstan-3β-11β-diol-17β-carboxylic acid for 4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylic acid (XX), yields methyl 4,4,14-trimethyl-5α-androstan-3β-11β-diol-17β-carboxylate (XXII).

**EXAMPLE 29**

**4,4,14-trimethyl-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylic acid**

Following the procedure set forth in Example 17, but substituting methyl-4,4,14-trimethyl-3β-acetoxy-Δ$^{11}$-5α-androstan-17β-carboxylate for methyl-3β-acetoxy-4,4,14-trimethyl-5α-androstan-11-one-17β-carboxylate (XIX), yields 4,4,14-trimethyl-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylic acid.

**EXAMPLE 30**

**Methyl 4,4,14-trimethyl-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylate**

Following the procedure set forth in Example 20, but substituting 4,4,14-trimethyl-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylic acid for 4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylic acid (XXI), yields methyl 4,4,14-trimethyl-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylate (XXII).

**EXAMPLE 31**

**4,4,14-trimethyl-5α-androstan-3β-17β-carboxylic acid**

Following the procedure set forth in Example 17 but substituting methyl-4,4,14-trimethyl-3β-acetoxy-5α-androstan-17β-carboxylate for methyl-3β-acetoxy-4,4,14-trimethyl-5α-androstan-11-one-17β-carboxylate (XIX), yields 4,4,14-trimethyl-5α-androstan-3β-ol-17β-carboxylic acid.

**EXAMPLE 32**

**Methyl 4,4,14-trimethyl-5α-androstan-3β-ol-17β-carboxylate**

Following the procedure set forth in Example 20, but substituting 4,4,14-trimethyl-5α-androstan-3β-ol-17β-carboxylic acid for 4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylic acid (XXI), yields methyl 4,4,14-trimethyl-5α-androstan-3β-ol-17β-carboxylic acid.

**EXAMPLE 33**

**Methyl 3-isopropylidene-14-methyl-A-nor-5α-androstan-11β-ol-17β-carboxylate**

Following the procedure set forth in Example 26 but substituting methyl-4,4,14-trimethyl-1α-androstan-3β-11β-diol-17β-carboxylate for methyl-4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylate (XXI), yields methyl 3-isopropylidene-14-methyl-A-nor-5α-androstan-11β-ol-17β-carboxylate (XXII).

**EXAMPLE 34**

**Methyl 3-isopropylidene-14-methyl-A-nor-Δ$^{11}$-5α-androstan-17β-carboxylate**

Following the procedure set forth in Example 26 but substituting methyl-4,4,14-trimethyl-A-nor-Δ$^{11}$-5α-androstan-3β-ol-17β-carboxylic acid for methyl-4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylate (XXI), yields methyl 3-isopropylidene-14-methyl-A-nor-Δ$^{11}$-5α-androstan-17β-carboxylate (XXII).

**EXAMPLE 35**

**Methyl 3-isopropylidene-14-methyl-A-nor-5α-androstan-17β-carboxylate**

Following the procedure set forth in Example 26, but substituting methyl-4,4,14-trimethyl-5α-androstan-3β-ol-17β-carboxylate for methyl-4,4,14-trimethyl-5α-androstan-3β-ol-11-one-17β-carboxylate (XXI), yields methyl 3-isopropylidene-14-methyl-A-nor-5α-androstan-17β-carboxylate (XXII).
EXAMPLE 36
3-isopropylidenec-14-methyl-A-nor-5a-androstan-1one-17b-carboxylic acid (XXIII)

A solution of 200 mg. of methyl 3-isopropylidenec-14methyl-A-nor-5a-androstan-11-one-17b-carboxylic acid (XXII) in 30 ml. of 5% methanolic KOH and 2 ml. of water is refluxed under nitrogen for 7½ hours. The mixture is then cooled to room temperature, acidified with glacial acetic acid and diluted with water. Recrystallization furnishes 183 mg. of 3-isopropylidenec-14-methyl-A-nor-5a-androstan-11-one-17b-carboxylic acid (XXIII) melting at 255-258°. The pure acid is obtained after recrystallization from 95% ethanol and has the following properties: M.P. 266-267°; [c]D25 +43° (c., .82 in chl.);

\[\lambda_{max} 3.07, 5.77, 5.89, 6.00a\]


EXAMLE 37
3-isopropylidenec-14-methyl-A-nor-5a-androstan11b-ol-17b-carboxylic acid


EXAMLE 38
3-isopropylidenec-14-methyl-A-nor-5a-androstan-11b-ol-17b-carboxylic acid


EXAMLE 39
3-isopropylidenec-14-methyl-A-nor-5a-androstan-17b-carboxylic acid

Following the procedure set forth in Example 36, but substituting methyl 3-isopropylidenec-14-methyl-A-nor-5a-androstan-17b-carboxylate for methyl 3-isopropylidenec-14-methyl-A-nor-5a-androstan-17b-carboxylate (XXII) yields 3-isopropylidenec-14-methyl-A-nor-5a-androstan-17b-carboxylic acid.

EXAMLE 40
Methyl 14-methyl-A-nor-5a-androstan-3,11-dione-17b-carboxylate (XXV)

A solution of 1.5 g. of methyl 3-isopropylidenec-14methyl-A-nor-5a-androstan-11-one - 17b-carboxylate (XXII) in 80 ml. of ethyl acetate is ozonized at -20° until a potassium iodide trap, placed behind the reaction vessel, shows the color of iodine. This requires 3.6 liters of gas containing .741 mmole of ozone per liter. The calculated amount for 1 mole of ozone per mole of substrate is 3.2 liters. The ozonolysis solution is then allowed to warm up to 0°, 3.5 ml. of glacial acetic acid is added and the ozonide decomposed reductively by the portionwise addition of 12 g. of zinc dust. After stirring for a total of 1 hour at room temperature the ozonide is completely decomposed as indicated by a negative starch iodide test. The mixture is then filtered, the ethyl acetate filtrate extracted with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline residue upon recrystallization from acetone-hexane yields 590 mg. of the pure methyl 14-methyl-A-nor-5a-androstan-3,11-dione-17b-carboxylate (XXV), an additional 280 mg. of (XXV) melting at 176-179°, and a third crop of 184 mg. of (XXV). The analytically pure methyl 14-methyl-A-nor-5a-androstan-3,11-dione-17b-carboxylate (XXV), obtained by recrystallization from acetone-hexane has the following properties: M.P. 178-180°; on cooling the sample resolidifies and then remelts at 216-218°. [c]D25 +5.5° (c., .64 in chl.);

\[\lambda_{max} 5.76, 5.85a\]

Analysis.—Calcd. for C₂₅H₃₃O₃ (436.45): C, 72.80; H, 8.73. Found: C, 72.75; H, 8.98.

EXAMLE 41
Methyl 14-methyl-A-nor-5a-androstan-11β-ol-3-one-17b-carboxylate (LXXXVIII)


EXAMLE 42
Methyl 14-methyl-A-nor-5a-androstan-3-one-17β-carboxylate (XC)


EXAMLE 43
Methyl 14-methyl-A-nor-5a-androstan-3-one-17β-carboxylate (LXVII)


EXAMLE 44
Methyl 14-methyl-A-nor-5b-androstan-3,11-dione-17β-carboxylate (XXVI)

A solution of 220 mg. of methyl-A-nor-5a-androstan3,11-dione-17β-carboxylate (XXV) in 12 ml. of .01 N KOH in methanol is allowed to remain at room temperature for ½ hour. The solution is neutralized with glacial acetic acid, diluted with water, concentrated in vacuo and extracted with chloroform. The chloroform extract is dried over sodium sulfate and evaporated to dryness in vacuo. The residue upon crystallization from methanol furnishes methyl 14-methyl-A-nor-5b-androstan-3,11-dione-17β-carboxylate (XXVI), melting at 220-222°. The analytically pure material has the following properties: M.P. 222-224°; [c]D25 +175° (c., .66 in chl.);

\[\lambda_{max} 5.74 and 5.86a\]

Analysis.—Calcd. for C₂₅H₃₃O₃ (346.45): C, 72.80; H, 8.73. Found: C, 72.85; H, 8.78.

EXAMLE 45
Methyl 14-methyl-A-nor-5b-androstan-3,11-dione-17β-carboxylate (XXVI)

A solution of 100 mg. of methyl 14-methyl-A-nor-5a-androstan-3,11-dione-17β-carboxylate (XXV) in 5 ml. of 0.1% HBr in glacial acetic acid is allowed to remain at room temperature for 10 minutes. The solution is neutralized with aqueous bicarbonate, diluted with water, concentrated in vacuo and extracted with chloroform. The chloroform extract is dried over sodium sulfate and evaporated to dryness in vacuo. The residue upon recrystallization from methanol furnishes methyl 14-methyl-A-nor-5b-androstan-3,11-dione-17β-carboxylate (XXVI).
EXAMPLE 46

Methyl 14-methyl-A-nor-5β-androstene-11β-ol-3-one-17β-carboxylate (LXXXVIII)


EXAMPLE 47

Methyl 14-methyl-A-nor-Δ⁷(11)5β-androstene-3-one-17β-carboxylate (XCV)


EXAMPLE 48

Methyl 14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylate (LVXVIII)


EXAMPLE 49

14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylic acid (XXVII)

To a mixture of 7.7 N KOH in methanol and 4.6 ml. of water, which has been refluxed for 10 minutes and cooled under a blanket of nitrogen, 460 mg. of methyl 14-methyl-A-nor-5α-androstane-3,11-dione-17β-carboxylate (XXV) and the resulting light yellow solution is refluxed for 7.5 hours under a blanket of nitrogen. The mixture is then cooled and after the addition of 5 ml. of glacial acetic acid is diluted with water. After removal of the bulk of the methanol in vacuo the 14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylic acid (XXVII) crystallizes and is filtered and washed with water. The 14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylic acid melts at 255-265°. The analytically pure 14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylic acid obtained after recrystallization from methanol and drying at 110° has the following properties: M.P. 270-272°; [α]D +184° (c. 1.04 in chloroform).

Analysis.—Calcd. for C₂₉H₃₇O₄: C, 71.10; H, 8.30. Found: C, 71.03; H, 8.37.

EXAMPLE 50

14-methyl-A-nor-5β-androstane-3,11-dione-17β-carboxylic acid (XXVII)


EXAMPLE 51

14-methyl-A-nor-5β-androstane-11β-ol-3-one-17β-carboxylic acid (LXXXIX)


EXAMPLE 52

14-methyl-A-nor-Δ⁷(11)5β-androstane-3-one-17β-carboxylic acid (XCI)


EXAMPLE 53

14-methyl-A-nor-5β-androstane-3-one-17β-carboxylic acid (LXIX)


EXAMPLE 54

Methyl 14-methyl-3-acetoxy-A-nor-Δ⁷(11)-androstane-11-one-17β-carboxylate (XLV)

A solution of 30 mg. of methyl 14-methyl-A-nor-5α-androstane-3,11-dione-17β-carboxylate (XXV) and 40 mg. of p-toluenesulfonic acid in 5 ml. of redistilled isopropyl acetate is slowly distilled under anhydrous conditions. One ml. is distilled off rapidly and a second milliliter over a 30 minute period. After a total of 45 minutes the mixture is cooled to room temperature, taken up in chloroform and the chloroform extract washed with dilute sodium bicarbonate and water, dried over sodium sulfate and taken to dryness in vacuo. 42 mg. of crude residue melting at 163-165° is triturated with ether and the resulting crystals (18 mg.) are recrystallized from methanol. The pure methyl 14-methyl-3-acetoxy-A-nor-Δ⁷(10)-androstane-11-one-17β-carboxylate (XLV) has the following properties: M.P. 170-171°; [α]D +124° (c. 0.38 in chloroform).

Analysis.—Calcd. for C₂₉H₃₇O₄: C, 71.10; H, 8.30. Found: C, 71.03; H, 8.37.

EXAMPLE 55

Methyl 14-methyl-3-acetoxy-A-nor-Δ⁷(10)-androstene-11-ol-17β-carboxylate


EXAMPLE 56

Methyl 14-methyl-3-acetoxy-A-nor-Δ⁷(10),17β-androstadiene-17β-carboxylate


EXAMPLE 57

Methyl 14-methyl-3-acetoxy-A-nor-Δ⁷(10)-androstene-17β-carboxylate

Following the procedure set forth in Example 54 but substituting methyl 14-methyl-A-nor-5α-androstane-17β-carboxylate for methyl 14-methyl-A-nor-5α-androstane-17β-carboxylate.
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3,11 - dione - 17β-carboxylate (XXV) yields methyl 14-methyl - 3 - acetoxycarbonyl-17β-carboxylate.

**EXAMPLE 58**

Methyl 14-methyl-3-acetoxycarbonyl-17β-carboxylate - 11-one-17β-carboxylate (XVII)


**EXAMPLE 59**

14-methyl-3-acetoxycarbonyl-17β-carboxylate - 11-one-17β-carboxylate (XVI)


**EXAMPLE 60**

14-methyl-3-acetoxycarbonyl-17β-carboxylate (XVI)


**EXAMPLE 61**

14 - methyl - 3 - acetoxycarbonyl-17β-carboxylate (XVI)


**EXAMPLE 62**

14 - methyl - 3 - acetoxycarbonyl-17β-carboxylate (XVI)


**EXAMPLE 63**

Methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII)

To a solution of 100 mg. of methyl 14-methyl-3-acetoxycarbonyl-17ß-carboxylate (XVI) in 18 ml. of dioxane and 6 ml. of a solution containing 1 ml. of 70% perchloric acid in 100 ml. of water, is added 100 mg. of N-bromosuccinimide. After 5 minutes the reaction is stopped by the addition of dilute sodium bisulfite solution until colorless and the methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII) is extracted with chloroform. The chloroform-dioxane extract is washed with dilute sodium bicarbonate and water, dried over sodium sulfate and the solvents removed in vacuo. The crystalline residue is essentially pure and melts at 159-160° with decomposition. The analytically pure sample of methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII) is obtained by recrystallization from acetone and has the following properties: M.P. 160-161°; [α]D20 +45° (c, 1.04 in chloroform).

**EXAMPLE 64**

Methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII)

Following the procedure set forth in Example 63, but substituting N-bromosuccinimide, dibromomethyl, or bromine for N-bromosuccinimide, yields methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII).

If an N-chloro compound such as N-chlorosuccinimide or an N-iodo compound such as N-iodoacetamide is used in place of N-bromosuccinimide in following the procedure of Example 56, there is obtained the corresponding methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate and methyl 14-methyl-5ß-iodo-A-nor-17ß-carboxylate, respectively.

**EXAMPLE 65**

Methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII)


Similarly, following the procedure of Example 63 but substituting N-chlorosuccinimide or N-iodoacetamide for N-bromosuccinimide there is obtained methyl 14-methyl-5ß-chloro-A-nor-androstane-11-one-17ß-carboxylate, respectively.

**EXAMPLE 66**

Methyl 14-methyl-5ß-bromo-A-nor-17ß-carboxylate (XXVII)

Following the procedure set forth in Example 63, but substituting methyl 14-methyl-3-acetoxycarbonyl-17ß-carboxylate for methyl 14-methyl-A-nor-17ß-carboxylate (XVII), and reducing the quantity of N-bromoacetamide from 100 mg. to 40 mg. yields methyl 14-methyl-5ß-bromo-A-nor-androstane-11-one-17ß-carboxylate.
formamide is heated on the steam bath for 2 hours. The cooled mixture is diluted with water, extracted with chloroform and the chloroform extract washed thoroughly with water. The chloroform extract is dried over sodium sulfate, evaporated to dryness in vacuo and the 55 mg. residue obtained is separated into the methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylic acid and methyl 14-methyl-A-nor-Δⁿ⁻β₅-androstene-3,11-dione-17β-carboxylate components by fractional crystallization. Crystallization first from ether then from methanol furnished, as the more insoluble component, the methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylate having the following properties: M.P. 223–224°C; [α]₅₂⁰° +90° (c, 0.59 in chloroform).

**EXAMPLE 69**

14-methyl-5β-bromo-A-nor-Δⁿ⁻α₄-androstene-3-one-17β-carboxylic acid

Following the procedure set forth in Example 63 but substituting 14-methyl-5β-acetoxy-A-nor-Δⁿ⁻α₄-androstene-11β,17β-dicarboxylic acid for methyl 14-methyl-3-acetoxy-A-nor-Δⁿ⁻α₄-androstene-11β,17β-dicarboxylic acid (XLV) and decreasing the amount of N-bromosuccinimide from 100 mg. to 40 mg. yields 14-methyl-5β-bromo-A-nor-Δⁿ⁻α₄-androstene-3-one-17β-carboxylic acid.

**EXAMPLE 70**

14-methyl-5β-bromo-A-nor-androstene-3-one-17β-carboxylic acid

Following the procedure set forth in Example 63, but substituting 14-methyl-5β-acetoxy-A-nor-Δⁿ⁻α₄-androstene-11β,17β-dicarboxylic acid for methyl 14-methyl-5β-acetoxy-A-nor-Δⁿ⁻α₄-androstene-11β,17β-dicarboxylic acid (XLV) and decreasing the amount of N-bromosuccinimide from 100 mg. to 40 mg. yields 14-methyl-5β-bromo-A-nor-Δⁿ⁻α₄-androstene-3-one-17β-carboxylic acid.

**EXAMPLE 71**

Methyl 14-methyl-5β-fluoro-A-nor-androstene-3,11-dione-17β-carboxylic acid (XLVII)

Into a solution of 50 mg. of methyl 14-methyl-3-acetoxy-A-nor-Δⁿ⁻α₄-androstene-11β,17β-dicarboxylic acid (XLV) in 3 ml. of pyridine and 7 ml. of dioxane maintained at 0°C with stirring, a stream of perchloric fluoride. After 3 minutes excess chloroform is added and the mixture is then extracted with water, dilute acid, sodium bicarbonate solution and again with water. The chloroform-dioxane extract is evaporated to dryness in vacuo and the resulting methyl 14-methyl-5β-fluoro-A-nor-androstene-3,11-dione-17β-carboxylic acid (XLII) recrystallized from acetone.

**EXAMPLE 72**

14-methyl-5β-fluoro-A-nor-androstene-3,11-dione-17β-carboxylic acid (XLVIII)


**EXAMPLE 73**

Methyl 14 - methyl - A - nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylic acid

A solution of 62.5 mg. of methyl 14-methyl-5β-bromo-A-nor-androstene-3,11-dione-17β-carboxylic acid (XLVII) and 125 mg. of lithium chloride in 4.5 ml. of dimethylformamide is heated on the steam bath for 2 hours. The cooled mixture is diluted with water, extracted with chloroform and the chloroform extract washed thoroughly with water. The chloroform extract is dried over sodium sulfate, evaporated to dryness in vacuo and the 55 mg. residue obtained is separated into the methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylate and methyl 14-methyl-A-nor-Δⁿ⁻β₅-androstene-3,11-dione-17β-carboxylate components by fractional crystallization. Crystallization first from ether then from methanol furnishes, as the more insoluble component, the methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylate having the following properties: M.P. 223–224°C; [α]₅₂⁰° +90° (c, 0.59 in chloroform).

**EXAMPLE 74**


A solution of 50 mg. of methyl 14-methyl-5β-bromo-A-nor-androstene-3,11-dione-17β-carboxylic acid (XLVII) in 1 ml. of collidine is refluxed for one hour. The reaction mixture is dissolved in chloroform and the resulting chloroform solution is extracted with 1 N hydrochloric acid. Concentration of the chloroform extract to dryness furnishes a mixture of methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstene-3,11-dione-17β-carboxylic acid (LIII) and methyl 14-methyl-A-nor-Δⁿ⁻β₅-androstene-3,11-dione-17β-carboxylate (XLIX), which may be separated into its individual components by fractional crystallization.

**EXAMPLE 75**


**EXAMPLE 76**

Methyl 14-methyl-A-nor-Δⁿ⁻α₄-androstadiene-3-one-17β-carboxylate and methyl 14-methyl-A-nor-Δⁿ⁻β₅-androstadiene-3-one-17β-carboxylate

EXAMPLE 77


EXAMPLE 78
14-Methyl-A-nor - Δ² - androstene-3,11-dione-17β-carboxylic acid (LIV) and 14-methyl-A-nor-Δ³-5β-androstadiene-3-one-17β-carboxylic acid (L)


EXAMPLE 79


EXAMPLE 80
14-methyl-A-nor-Δ³,11β-(androstadiene-3-one-17β-carboxylic acid and 14-methyl-A-nor-Δ³,11β-(5β-androstadiene-3-one-17β-carboxylic acid


EXAMPLE 81
14-methyl-A-nor - Δ² - androstene-3-one-17β-carboxylic acid and 14-methyl-A-nor-Δ³-5β-androstene-3-one-17β-carboxylic acid


EXAMPLE 82
Methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI)

To a suspension of 210 mg. of methyl 14-methyl-A-nor-5α-androstan-3,11-dione-17β-carboxylate (XXV) in 2 ml. of glacial acetic acid is added .08 mL of 6% hydrogen bromide in glacial acetic acid. The crystals dissolve immediately upon addition of the mineral acid. A bromine solution consisting of .2 mmole of bromine and .2 mmole of anhydrous sodium acetate per milliliter of glacial acetic acid is then added (3.3 mL) followed by the addition of .8 mL of 6% hydrogen bromide in glacial acetic acid. Decolorization of the bromo compound is immediately accompanied by a precipitation of the methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI). After the addition of 2 mL of water the crystals are filtered and dried. There is obtained 89 mg. of methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI), which after recrystallization from methanol has the following properties: M.P. 194° and 195° with decomposition: [α]D-23° +90° (c., 65 in chl.);

Molar rotation: 5.72°, 5.75° and 5.88°


Found: C, 59.48; H, 6.77.

The acetic acid-water filtrate from the methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI) is diluted further with water, extracted with chloroform and the chloroform extract washed thoroughly with water, bicarbonate and again with water. The chloroform extract is dried over sodium sulfate, evaporated to dryness and fractionally crystallized from methanol. There is obtained an additional 65 mg. of the methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI) in the first crop, and by concentration of the mother liquors, 17 mg. of methyl 14-methyl-5β-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (XLVII), having an M.P. of 160°. This latter material was identified by mixture melting point and infrared comparison. Optical rotatory dispersion: first extremum [α]D-20°-506°.

EXAMPLE 83
Methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LII)


EXAMPLE 84
14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylic acid (LII)


EXAMPLE 85
Methyl 14-methyl-A-nor-Δ²-androstan-3,11-dione-17β-carboxylate (LIIII)

A solution of 170 mg. of methyl 14-methyl-5α-bromo-A-nor-androstan-3,11-dione-17β-carboxylate (LI) and 1.5 g. of lithium bromide in 13.5 ml. of dimethylformamide is heated on the steam bath for 2 hours. The resulting mixture is diluted with water, the mixture ex-
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tracted with chloroform, and the chloroform extract washed with water and sodium bicarbonate, dried over sodium sulfate and evaporated to dryness in vacuo. The residue weighing 135 mg. yields crystallization from methanol 86 mg. of pure methyl 14-methyl-A-nor-Δ^5-androstene-3,11-dione-17β-carboxylate (LIII) melting at 202–203°;

\[ \lambda_{	ext{max}} 240 \text{ m} \mu \ (\epsilon = 9,600). \]

**EXAMPLE 86**

14-methyl-A-nor-Δ^5-androstene-3,11-dione-17β-carboxylic acid (LIV)

A solution of 16 mg. of methyl 14-methyl-A-nor-Δ^5-androstene-3,11-dione-17β-carboxylate (LIII) in 3.75 ml. of 7 N methanolic potassium hydroxide and 2.5 ml. of water that has been refluxed and cooled under helium is refluxed under a blanket of helium for 7 hours. The mixture is then acidified with glacial acetic acid, diluted with water and extracted with chloroform. The chloroform extract is washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline residue after recrystallization from methanol yields 14 - methyl - A - nor - Δ^5 - androstene - 3,11 - dione - 17β-carboxylic acid (LIV) having the following properties:

\[ \lambda_{	ext{max}} 241 \text{ m} \mu \ (\epsilon = 7,600); \lambda_{	ext{max}} 5.75, 5.86 \text{ and } 6.00 \mu \]

**EXAMPLE 87**

14-methyl-A-nor-Δ^5-5p-androstene-3,11-dione-17β-carboxylic acid (L)

Following the procedure set forth in Example 86 but substituting methyl 14-methyl-A-nor-Δ^5-5p-androstene-3,11-dione-17β-carboxylate (XLIX) for methyl 14-methyl-A

\[ \lambda_{	ext{max}} 241 \text{ m} \mu \ (\epsilon = 7,600); \lambda_{	ext{max}} 5.75, 5.86 \text{ and } 6.00 \mu \]

**EXAMPLE 88**

14-methyl-A-nor-Δ^5-androstene-11β-ol-3-one-17β-carboxylic acid


**EXAMPLE 89**

14-methyl-A-nor-Δ^5-5p-androstene-11β-ol-3-one-17β-carboxylic acid


**EXAMPLE 90**

14-methyl-A-nor-Δ^5(11)-androstadiene-3-one-17β-carboxylic acid


**EXAMPLE 91**

14-methyl-A-nor-Δ^5(11)-5p-androstadiene-3-one-17β-carboxylic acid


**EXAMPLE 92**

14-methyl-A-nor-Δ^5-3-one-17β-carboxylic acid


**EXAMPLE 93**

14-methyl-A-nor-Δ^5-5p-androstene-3-one-17β-carboxylic acid


**EXAMPLE 94**

Methyl 14-methyl-3,3-ethylenedioxy-A-nor-Δ^5-androstene-11-one-17β-carboxylate (CXXIV) and methyl 14-methyl-3,3-ethylenedioxy-A-nor-Δ^5-androstene-11-one-17β-carboxylate (CXXVI)

To a stirred mixture of 133 ml. of benzene, 20 ml. of ethylene glycol and 266 mg. of p-toluene sulfonic acid, which has been refluxed for 1 hour with the aid of a Dean-Stark separator is added 200 mg. of methyl-A-nor-Δ^5-androstene-3,11-dione-17β-carboxylate (LIII) and the resulting mixture is continued at reflux for 6 hours. The mixture is then cooled, neutralized rapidly by the addition of excess sodium bicarbonate, diluted with water and the layers separated. The aqueous layer is washed again with benzene and the combined benzene extracts dried over sodium sulfate. Evaporation of the solvent in vacuo produces a crystalline residue, which on recrystallization from methanol furnishes 103 mg. of the pure methyl 14 - methyl - 3,3-ethylenedioxy-A-nor-Δ^5-androstene-11-one-17β-carboxylate (CXXIV) possessing the following properties: needles M.P. 143–144°; [α]_23 +153° (c. .83 in chlfr.);

\[ \lambda_{	ext{max}} 5.70, 5.87. \]

**Analysis.—** Calcd. for C_{24}H_{32}O_5 (388.49): C, 71.10; H, 8.30. Found: C, 71.11; H, 8.30.

**EXAMPLE 95**

Methyl 14-methyl-3,3-ethylenedioxy-A-nor-5β-androstene-11-one-17β-carboxylate (CXLVII)

Following the procedure set forth in Example 94 but substituting methyl 14-methyl-A-nor-5β-androstene-3,11-dione-17β-carboxylate (XXVI) for the methyl 14-methyl-A-nor-Δ^5-androstene-3,11-dione-17β-carboxylate (LIII) there is obtained methyl 14-methyl-3,3-ethylenedioxy-A-nor-5β-androstene-3,11-dione-17β-carboxylate (CXLVIII) which after crystallization from methanol, has the following properties: M.P. 189–190°; [α]_23 +67° (c. .6 in chlfr.);

\[ \lambda_{	ext{max}} 5.77, 5.88. \]

**Analysis.—** Calcd. for C_{24}H_{32}O_5: C, 70.74; H, 8.72. Found: C, 70.74; H, 8.82.
EXAMPLE 97
14-methyl-3,3-ethylenedioxo-A-nor-Δ^4 - androstene - 11 - one - 17β-carboxylic acid (CXXVII)

Following the procedure set forth in Example 96 but substituting methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4-androstene-11-one-17β-carboxylate for the methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4-androstene-11-one-17β-carboxylate there is obtained methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4-androstene-11-one-17β-carboxylic acid which after crystallization from methanol has the following properties: M.P. 237-238°; [x]_p +20° (c, 54).

Analysis—Found: C, 70.12; H, 8.43.

EXAMPLE 98
14-methyl-A-nor-Δ^4-androstene-3,11-dione-17β-carboxylic acid (LIV)

A solution of 25 mg. of 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4 - androstene - 11 - one - 17β - carboxylic acid (XXXIIIb) in 5 ml of methanol and 17 ml of 8% sulfuric acid is refluxed for 2 hours. After cooling to room temperature the mixture is diluted with water, taken up in chloroform, the chloroform solution washed with water, dried over sodium sulfate and taken to dryness in vacuo. The residue weighing 20 mg. on recrystallization from methanol furnishes the pure 14-methyl-A-nor-Δ^4-androstene-3,11-dione-17β-carboxylic acid (LIV) possessing the following properties: M.P. 296-299°; λ max. 240μ (ε, 4,000); λ max. 5.76, 5.88 and 6.0μ μ.

EXAMPLE 99
Methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4-androstene-11β-ol-17β-carboxylate (CXXIX)

A solution of 14 mg. of methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4 - androstene-11β-ol-17β-carboxylate (XXXIIId) and 16 mg. of lithium borohydride in 2 ml of freshly distilled tetrahydrofuran is stirred at room temperature for 18 hours. At the end of this period excess borohydride is destroyed by the careful addition of water. The diluted solution is extracted with chloroform, the chloroform extract washed with water, dried over sodium sulfate and the solvent removed in vacuo. The residue containing the methyl 14-methyl-3,3-ethylenedioxo-A-nor-Δ^4-androstene-11β-ol-17β-carboxylate (XXXIV) on crystallization from methanol furnishes the pure compound possessing the following properties: M.P. 226-228°; [x]_D +116° (c, 511).

Analysis—Calcd. for C_{25}H_{34}O_{3}: C, 70.74; H, 8.78. Found: C, 70.76; H, 8.78.
EXAMPLE 106

Methyl 14-methyl-4-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLIII)

A solution of 20 mg. of methyl 14-methyl-3,3-ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylic acid in 2 ml. of 80% glacial acetic acid is allowed to stand at room temperature for 2 hours. After removal of the solvents in vacuo at room temperature the residue (18 mg.) is recrystallized from methanol. It represents the pure methyl 14 - methyl - A - nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylate possessing the following properties: M.P. 165–167°; [α]D⁵³ + 214° (c., 68 in chloroform); no selective absorption in the ultraviolet;

λ⁵⁷⁴m 5.74μ

EXAMPLE 107

Methyl 14α-methyl-A-nor-Δ⁴-androstene-3,11-dione-17β-carboxylic acid (CXXIX)

Following the procedure set forth in Example 106 but substituting methyl 14α-methyl-3,3-ethylenedioxy-A-nor-Δ⁴ - androstene - 11 - one-17β-carboxylate for methyl 14-methyl - 3,3 - ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylic acid, there is obtained methyl 14α-methyl-A-nor-Δ⁴-androstene-3,11-dione-17β-carboxylate, which on recrystallization from methanol furnishes crystals of the following properties: M.P. 171–174°; [α]D + 300°;

λ⁵⁷⁴m 5.74, 5.84μ (2 Ci)

Similarly, applying the above reaction to methyl 14-methyl - 3,3 - ethylenedioxy-A-nor-Δ⁴-androstene-11β-ol-17β-carboxylate there is obtained methyl 14-methyl-A-nor-Δ⁴-androstene-11β-ol-3-one-17β-carboxylate.

EXAMPLE 108

Methyl 14α-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLVI)

A solution of 20 mg. of methyl 14α-methyl-3,3-ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylate in 2½ ml. 1.13 N perchloric acid in methanol alcohol is heated under reflux on the steam bath for 4 hours. After cooling the mixture is neutralized with sodium bicarbonate, extracted with chloroform and the chloroform extract washed with water. Evaporation of the sodium sulfate dried solution in vacuo yields the desired methyl 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylate as a crystalline residue.

EXAMPLE 109

14-methyl-3,3-ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylic acid (CXXXIX)


EXAMPLE 110

14-methyl-3,3-ethylenedioxy-A-nor-Δ⁴-androstene-11β-ol-17β-carboxylic acid (CXXXII)


EXAMPLE 111

14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLIII)

Following the procedure set forth in Example 106 but substituting 14-methyl-3,3-ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylic acid for methyl 14-methyl-3,3 - ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-17β-carboxylate yields 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLIII).

EXAMPLE 112

14-methyl-A-nor-Δ⁵-androstene-3,11-dione-17β-carboxylic acid (CXXVIII)


EXAMPLE 113

14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLII)


EXAMPLE 114

14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid (CXLII)

Following the procedure set forth in Example 96, but substituting methyl 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylate for methyl 14-methyl-3,3-ethylenedioxy-A-nor-Δ⁵,Δ⁶(11),androstadiene-11,17β-carboxylic acid yields 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3-one-17β-carboxylic acid.

EXAMPLE 115

14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid chloride (XXVIII)

To a suspension of 290 mg. of vacuum-dried 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid (XXVII) in 25 ml. of anhydrous benzene is added with stirring 2.70 ml. of redistilled oxalyl chloride. After 30 minutes all the acid has dissolved and the solution is allowed to remain at room temperature for an additional 40 minutes. Upon removal of the solvent in vacuo there remains a crystalline solid to which is added 2 ml. of anhydrous benzene and the latter removed again in vacuo, thus yielding 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid chloride (XXVIII).

EXAMPLE 116

14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid chloride (LV)

Following the procedure set forth in Example 115 but substituting 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid chloride (LV) for 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid (XXVII) yields 14-methyl-A-nor-Δ⁵,Δ⁶(11),androstadiene-3,11-dione-17β-carboxylic acid chloride (LV).

**EXAMPLE 118**

14-methyl-A-nor-Δ^1-5β-androstene-11β-ol-3-one-17β-carboxylic acid chloride


**EXAMPLE 119**

14-methyl-A-nor-Δ^1-5β-androstene-11β-ol-3-one-17β-carboxylic acid chloride


**EXAMPLE 120**

14-methyl-A-nor-5β-androstene-11β-ol-3-one-17β-carboxylic acid chloride


**EXAMPLE 121**

14-methyl-A-nor-Δ^8-9(11)-androstadiene-3-one-17β-carboxylic acid chloride


**EXAMPLE 122**

14-methyl-A-nor-Δ^1-9(9)-5β-androstadiene-3-one-17β-carboxylic acid chloride


**EXAMPLE 123**

14-methyl-A-nor-Δ^8(8)-5β-androstene-3-one-17β-carboxylic acid chloride


**EXAMPLE 124**

14-methyl-A-nor-Δ^2-9(9)-5β-androstadiene-3-one-17β-carboxylic acid chloride


**EXAMPLE 125**

14-methyl-A-nor-Δ^1-5β-androstene-3-one-17β-carboxylic acid chloride


**EXAMPLE 126**

14-methyl-A-nor-5β-androstane-3-one-17β-carboxylic acid chloride


**EXAMPLE 127**

14-methyl-A-nor-Δ^8-9(11)-androstadiene-3-one-17β-carboxylic acid chloride


**EXAMPLE 128**

14-methyl-A-nor-Δ^-9β-11-dione-17β-carboxylic acid chloride


**EXAMPLE 129**

14-methyl-A-nor-Δ^-9β-androstene-11β-ol-3-one-17β-carboxylic acid chloride


**EXAMPLE 130**

14-methyl-3,3-ethylenedioxy-A-nor-Δ^-9-androstene-11-one-17β-carboxylic acid chloride (CXXXVI)

To a solution of 11 mg of 14-methyl-3,3-ethylenedioxy-A-nor-Δ^-9-androstene-11-one-17β-carboxylic acid in 2 ml of anhydrous benzene is added .2 ml of oxalyl chloride. Evolution of carbon monoxide and carbon dioxide occurs and the reaction is allowed to proceed at room temperature for ½ hour when the evolution of gas has subsided. Evaporation of the solvent in vacuo under strictly anhydrous conditions leaves the crude 14-methyl-3,3-ethylenedioxy-A-nor-Δ^-9-androstene-11-one-17β-carboxylic acid chloride (CXXXVI), melting at 140-150°. Similarly, treating 14-methyl-3,3-ethylenedioxy-A-nor-Δ^-9-androstene-11-one-17β-carboxylic acid according to the procedure of Example 121, yields 14-methyl-3,3-ethylenedioxy-A-nor-Δ^-9-androstene-11-one-17β-carboxylic acid chloride.

**EXAMPLE 131**

14-methyl-3,3-ethylenedioxy-A-nor-5β-androstan-11-one-17β-carboxylic acid chloride

Following the procedure set forth in Example 130 but substituting 14-methyl-3,3-ethylenedioxy-A-nor-5β-androstan-11-one-17β-carboxylic acid for 14-methyl-3,3-ethyl-

**EXAMPLE 132**

14-methyl-3,3-ethylenedioxy-A-nor-5\(\beta\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylic acid chloride (CLIV)


**EXAMPLE 133**

14-methyl-3,3-ethylenedioxy-A-nor-D\(^\Delta\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylic acid chloride (CXXXV)


**EXAMPLE 134**

14-methyl-3,3-ethylenedioxy-A-nor-D\(^\Delta\)(11)-androstadiene-17\(\beta\)-carboxylic acid chloride


**EXAMPLE 135**

14-methyl-3,3-ethylenedioxy-A-nor-D\(^\Delta\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylic acid chloride


**EXAMPLE 136**

Sodium 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11-one-17\(\beta\)-carboxylate (XXIV)

130 mg. of 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11-one-17\(\beta\)-carboxylic acid (XXII) is dissolved carefully in 4 ml. of 1 N sodium hydroxide. When all the material has gone into solution the pH has reached 8.0. The solution is then diluted with 16 ml. of water, lyophilized and subsequently dried at 110\(^\circ\) in high vacuum, yielding the sodium 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11-one-17\(\beta\)-carboxylate (XXIV).

**EXAMPLE 137**

Sodium 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylate

Following the procedure set forth in Example 136 but substituting 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylic acid, for 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11-one-17\(\beta\)-carboxylic acid (XXII) yields sodium 14-methyl-3-isopropylidene-A-nor-5\(\alpha\)-androstone-11\(\beta\)-ol-17\(\beta\)-carboxylate.

**EXAMPLE 138**

Sodium 14-methyl-3-isopropylidene-A-nor-D\(^\Delta\)(11)-5\(\alpha\)-androste-17\(\beta\)-carboxylate

Following the procedure set forth in Example 136 but substituting 14-methyl-3-isopropylidene-A-nor-D\(^\Delta\)(11)-5\(\alpha\)-androste-17\(\beta\)-carboxylate.
The mixture is allowed to warm up to room temperature and after a total reaction time of 1½ hours it is filtered from flocculent polyethylene and evaporated to dryness in vacuo. The resulting yellow crystalline residue is recrystallized from methanol and furnishes 226 mg. of the pure 14-methyl-21-diazao-A-nor-5β-pregnane-3,11,20-trione (XXXIX) possessing the following properties: M.P. 173°C with decomposition and resolidifying at 204°C; [a]D23 = +250° (c, 1.1 in chlorf.).

\[ \text{Analysis—Caled. for C}_{29}\text{H}_{38}\text{O}_{2}N_{2} (356.45): C, 70.76; H, 7.92. Found: C, 70.54; H, 8.19.} \]

**EXAMPLE 145**


**EXAMPLE 146**


**EXAMPLE 147**


**EXAMPLE 148**


**EXAMPLE 149**


**EXAMPLE 150**


EXAMPLE 159
14-methyl-21-diaz-A-nor-∆³β(11),pregnadiene-3,20-dione


EXAMPLE 160

A solution of 14-methyl-3,3,3,5,5-pentamethylenedioxy-A-nor-Δ³-androsten-11-one 17β-carboxylic acid chloride in 4 ml. of anhydrous benzene is added to 10 ml. of a twice distilled solution of diazomethane at 0°. The reaction is allowed to remain at 0° for 2 hours, after which time the solvents are removed in vacuo, yielding 14 mg. of the 21-diaz -14-methyl-3,3,3,5,5-pentamethylenedioxy-A-nor-Δ³-pregnene-11,20-dione (CXXIX).


EXAMPLE 161


EXAMPLE 162


EXAMPLE 163


EXAMPLE 164
21-diaz-14-methyl-3,3,3,5,5-pentamethylenedioxy-A-nor-Δ³β(11)pregnadiene-20-one


EXAMPLE 165
21-diaz-14-methyl-3,3,3,5,5-pentamethylenedioxy-A-nor-Δ³β(11)pregnadiene-11β-ol-20-one (CXXVIII)


EXAMPLE 166
4,4,4-trimethyl-17β-hydroxymethyl-5α-androstan-3β,11β-diol

A solution of 50 mg. of methyl 4,4,4-trimethyl-3β-acetoxy-5α-androstan-11-one 17β-carboxylate (XIX) and 50 mg. of lithium aluminum hydride in 3 ml. of freshly distilled tetrahydrofuran is heated under reflux for 2 hours. After the decomposition of excess lithium aluminum hydride by the addition of saturated sodium sulfate solution, the mixture is extracted with chloroform, the chloroform extract washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The residual material (50 mg.) on recrystallization from methanol gives the analytically pure 4,4,4-trimethyl-17β-hydroxymethyl-5α-androstan-3β,11β-diol possessing the following properties: M.P. 234°-235°; [α]D +37° (c., 0.28 in dioxane); λmax 310μ (broad)

Analysis.—Calcd. for C23H32O2½H₂O: C, 73.95; H, 11.07. Found (after drying to constant weight at 140°): C, 73.72; H, 10.70.

EXAMPLE 167

To a solution of 80 mg. of 14-methyl-21-diaz-A-nor-5β-pregnane-3,11,20-trione (XXIX) was added at 0° 4 ml. of a saturated solution of hydrogen chloride in chloroform. The mixture is allowed to remain at 0° for 20 minutes after which time it was extracted with dilute sodium bicarbonate. The chloroform extract is dried over sodium sulfate, evaporated to dryness and the residual crystals (95 mg.) recrystallized from methanol. 82 mg. of the pure 14-methyl-21-chloro-A-nor-5β-pregnane-3,11,20-trione (XXX) is obtained, which possesses the following properties: M.P. 176°-177°; [α]D +194° (c., 1.06 in chf.);

λmax 5.75, 5.77 (shoulder). 5.87μ


EXAMPLE 168


EXAMPLE 169


EXAMPLE 170

14-methyl-21-chloro-A-nor-Δ⁵(11)-5β-pregnene-3,20-dione (CIV)


Similarly, following the procedure of Example 170 but substituting hydrogen bromide or hydrogen iodide for the hydrogen chloride, 14-methyl-21-bromo-A-nor-Δ⁵(11)-5β-pregnene-3,20-dione, and 14-methyl-21-iodo-A-nor-Δ⁵(11)-5β-pregnene-3,20-dione respectively are obtained.

EXAMPLE 171


Similarly, following the procedure of Example 171 but substituting hydrogen bromide or hydrogen iodide for the hydrogen chloride, 14-methyl-21-bromo-A-nor-5β-pregnene-3,20-dione and 14-methyl-21-iodo-A-nor-5β-pregnene-3,20-dione respectively, are obtained.

EXAMPLE 172

14-methyl-21-chloro-A-nor-Δ⁵-pregnene-3,11,20-trione (XLI)


EXAMPLE 173

14-methyl-21-chloro-A-nor-Δ⁵-5β-pregnene-3,11,20-trione (LIX)


EXAMPLE 174


EXAMPLE 175

14-methyl-21-chloro-A-nor-Δ⁵-5β-pregnene-11β-ol-3,20-dione (C)


EXAMPLE 176


EXAMPLE 177

14-methyl-21-chloro-A-nor-Δ⁵(11)-5β-pregnadiene-3,20-dione (CXII)


EXAMPLE 178


EXAMPLE 179

14-methyl-21-chloro-A-nor-Δ⁵-5β-pregnene-3,20-dione (LXXIV)

Following the procedure set forth in Example 167 but substituting 14-methyl-21-diaz-A-nor-Δ⁵-5β-pregnene-3,20-dione respectively, are obtained.

**EXAMPLE 187**


**EXAMPLE 188**


**EXAMPLE 189**


**EXAMPLE 190**


**EXAMPLE 191**

14-methyl-3-isopropylidene-A-nor-5α-pregnene-11,20-dione (LXIV)

A solution of 14-methyl-3-isopropylidene-A-nor-5α-pregnene-11,20-dione (LXIII) in 3 ml. of absolute benzene is added to an ethereal solution of dimethyl cadmium prepared from 900 mg. of cadmium chloride and methyl magnesium bromide formed in turn by the reaction of 210 mg. of magnesium with methyl bromide. The reaction mixture is refluxed for 1 hour and after cooling the excess of dimethyl cadmium is destroyed by the addition of 10% acetic acid. Chloroform is added, the layers are separated and the chloroform extract dried over sodium sulfate. Evaporation of the solvent in vacuo leaves the 14-methyl-3-isopropylidene-A-nor-5α-pregnene-11,20-dione (LXIV) as a crystalline solid.

**EXAMPLE 192**

14-methyl-3-isopropylidene-A-nor-5α-pregnene-11β-ol-20-one

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\[
57 \\
\text{ylic acid chloride yields 14-methyl-3-isopropylidene - A-nor-5a-pregnane-11\beta-ol-20-one.}
\]

**EXAMPLE 193**

\[
14\text{-methyl-3-isopropylidene-A-nor-5\alpha-pregnene-20-one}
\]

Following the procedure set forth in Example 191 but substituting 14-methyl-3-isopropylidene-A-nor-5\alpha-pregnane-11\beta,17\alpha-carboxylic acid chloride for 14-methyl-3-isopropylidene-A-nor-5a-pregnane-11\beta,17\alpha-carboxylic acid chloride yields 14-methyl-3-isopropylidene-A-nor-5\alpha-pregnene-20-one.

**EXAMPLE 194**

\[
14\text{-methyl-3-isopropylidene-A-nor-5a-pregnene-20-one}
\]

Following the procedure set forth in Example 191 but substituting 14-methyl-3-isopropylidene-A-nor-5a-pregnane-11\beta,17\alpha-carboxylic acid chloride for 14-methyl-3-isopropylidene-A-nor-5a-pregnane-11\beta,17\alpha-carboxylic acid chloride yields 14-methyl-3-isopropylidene-A-nor-5a-pregnene-20-one.

**EXAMPLE 195**

\[
14\text{-methyl-A-nor-5\beta-pregnene-3,11,20-trione (XXXIII)}
\]

To a solution of 100 mg. of 14-methyl-21-diazo-A-nor-5\beta-pregnane-3,11,20-trione (XXXI) in 10 ml. of chloroform is added under a blanket of carbon dioxide 1.5 ml. of freshly distilled aqueous hydrochloric acid. The mixture is thoroughly mixed by shaking for 3 minutes at room temperature, poured into water and chloroform and the chloroform solution extracted with dilute sodium bicarbonate with the aid of a small amount of sodium bisulfite. The chloroform extract is then washed with water, dried over sodium sulfate and evaporated to dryness in vacuo.

The 90 mg. of obtained residue crystallizes readily from methanol and furnishes 78 mg. of pure 14-methyl-A-nor-5\beta-pregnene-3,11,20-trione (XXXIII) possesses the following properties: M.P. 220-221^oC; [a]_D^20 +223^o (c, 1.06 in chlor.).

\[
\lambda_{max} \text{ 5.75 and 5.88\mu}
\]

**Analysis.**—Calcd. for C_{24}H_{34}O_3: C, 76.32; H, 9.15. Found: C, 76.29; H, 9.13.

**EXAMPLE 196**

\[
14\text{-methyl-A-nor-\Delta^5-pregnene-3,11,20-trione (XLIV)}
\]


**EXAMPLE 197**

\[
14\text{-methyl-A-nor-\Delta^5-5\beta-pregnene-3,11,20-trione (LXII)}
\]


**EXAMPLE 198**

\[
14\text{-methyl-A-nor-\Delta^5-pregnene-11\beta-ol-3,20-dione (CXIX)}
\]


**EXAMPLE 199**

\[
\Delta^5\text{-pregnene-11\beta-ol-3,20-dione in Example 198 yields 14-methyl-A-nor-\Delta^5-pregnene-11\beta-ol-3,20-dione (XCIX).}
\]

**EXAMPLE 200**

\[
14\text{-methyl-A-nor-5\beta-pregnene-11\beta-ol-3,20-dione (XCV)}
\]


**EXAMPLE 201**

\[
14\text{-methyl-A-nor-\Delta^5(11)-pregnadiene-3,20-dione (CXIX)}
\]


**EXAMPLE 202**

\[
14\text{-methyl-A-nor-\Delta^5(11)-5\beta-pregnadiene-3,20-dione (CXV)}
\]


**EXAMPLE 203**

\[
14\text{-methyl-A-nor-\Delta^5(11)-5\beta-pregnadiene-3-20-dione (CXII)}
\]


**EXAMPLE 204**

\[
14\text{-methyl-A-nor-\Delta^5-pregnene-3,20-dione (LXXX)}
\]


**EXAMPLE 205**

\[
14\text{-methyl-A-nor-\Delta^5-5\beta-pregnene-3,20-dione (LXXVII)}
\]


**EXAMPLE 206**

\[
14\text{-methyl-A-nor-5\beta-pregnene-3,20-dione (LXXXIII)}
\]

EXAMPLE 207

14α-methyl-A-nor-5α-pregnane-3,11,20-trione (LXV)

A solution of 14-methyl-3-isopropyliden-3A-nor-5α-pregnane-11β,20-dione in chloroform is ozonized in accordance with the procedure set forth in Example 40. The resulting 14α-methyl-A-nor-5α-pregnane-3,11,20-trione is obtained in crystalline form.

EXAMPLE 208

14α-methyl-A-nor-5α-pregnene-11β,ol-3,20-dione (XCX)


EXAMPLE 209

14α-methyl-A-nor-Δ(11)5α-pregnane-3,20-dione (CVII)


EXAMPLE 210

14α-methyl-A-nor-5α-pregnene-3,20-dione (LXXIII)


EXAMPLE 211

14α-methyl-A-nor-5β-pregnene-3,11,20-trione (XXXIII)

14α-methyl-A-nor-5α-pregnene-3,11,20-trione is isomerized by treatment with 0.02 NaOH, in accordance with the procedure set forth in Example 44, thus yielding 14α-methyl-A-nor-5β-pregnene-3,11,20-trione (XXXIII).

EXAMPLE 212

14α-methyl-A-nor-5β-pregnene-11β,ol-3,20-dione (XCX)


EXAMPLE 213

14α-methyl-A-nor-Δ(11)5β-pregnene-3,20-dione (CVII)


EXAMPLE 214

14α-methyl-A-nor-5β-pregnene-3,20-dione (LXXIII)


EXAMPLE 215

14α-methyl-A-nor-Δ(11)5β-pregnene-3,11,20-trione (XLIV)

A solution of 10 mg of 21-diazo-14-methyl-3β-ethylendioxy-A-nor-Δ(11)5β-pregnene-11β,20-dione in 3.3 ml of chloroform is shaken vigorously for 5 minutes with 0.5 ml of distilled constant boiling hydrogen iodide solution with the exclusion of air. The resulting mixture is poured into dilute sodium bicarbonate solution and the steroid extracted with chloroform. The chloroform extract is washed with dilute sodium bisulfite solution and water, dried over sodium sulfate and evaporated to dryness in vacuo. The 9 mg of residual crystalline material obtained, on recrystallization from methanol furnishes the pure 14α-methyl-A-nor-Δ(11)5β-pregnene-3,11,20-trione (XLIV) melting at 200-202°C; λاهيم 5.81, 5.88 and 6.03μ.


EXAMPLE 216

14α-methyl-A-nor-5β-pregnene-3,11,20-trione (XXXIII)


EXAMPLE 217

14α-methyl-A-nor-5β-pregnene-11β,ol-3,20-dione (XCIV)


EXAMPLE 218

14α-methyl-A-nor-5β-pregnene-11β,ol-3,20-dione (CXIX)


EXAMPLE 219

14α-methyl-A-nor-Δ(11)5β-pregnadiene-3,20-dione (CXIX)


EXAMPLE 220

14α-methyl-A-nor-5β-pregnadiene-21-ol-3,11,20-trione 21-acetate (XXXI)

A solution of 50 mg of 14-methyl-21-diazo-A-nor-5β-pregnadiene-3,11,20-trione (XXXI) in 3 ml of glacial acetic acid is heated on the steam bath for ½ hour. Water and chloroform are added and the resulting chloroform extract washed with sodium bicarbonate and water, dried over sodium sulfate and the solvent evaporated to dryness in vacuo. The 51 mg of residual crystals obtained after recrystallization from methanol furnishes 40 mg of the pure 14-methyl-A-nor-5β-pregnadiene-21-ol-3,11,20-trione-21-acetate (XXXI) possessing the following properties: M.P. 227-229° and 235-236°; cαgeh 47.3 +199° (c, .57 in chif); λاهيم 5.70, 5.78, 5.86 and 8.26μ.

Analysis.—Calcd. for C22H34O2: C, 71.10; H, 8.30. Found: C, 70.96; H, 8.34. Similarly, substituting propionic acid, butyric acid or other fatty acids for the acetic acid employed in the practice of Example 220, there are obtained the corresponding propionic, butyric and other esters, of 14-methyl-A-nor-5β-pregnadiene-21-ol-3,11,20-trione.
EXAMPLE 221
14-methyl-A-nor-Δ5-pregnene-12-ol,3,11,20-trione
21-acetate (XLII)


EXAMPLE 222
14-methyl-A-nor-Δ5-5β-pregnene-21-ol,3,11,20-trione
21-acetate (LX)


EXAMPLE 223
21-acetate (XCVII)


EXAMPLE 224
21-acetate (CI)


EXAMPLE 225
21-acetate (XCVIII)


EXAMPLE 226
41-methyl-A-nor-Δ5β(11)-pregniadiene-21-ol,3,20-dione
21-acetate (CV)


EXAMPLE 227
21-acetate (CXIII)


EXAMPLE 228
14-methyl-A-nor-Δ5β(11)-5β-pregnene-21-ol,3,20-dione
21-acetate (CV)

of acetone is refluxed for 20 hours. After cooling, the mixture is diluted with water, the bulk of the acetone removed in vacuo and the resulting crystalline suspension extracted with chloroform. The chloroform extract is dried over sodium sulfate and evaporated to dryness in vacuo. The resulting residue upon crystallization from methanol furnishes the pure 14-methyl-A-nor-5β-pregnane-21-ol-3,11,20-trione 21-acetate (XXIX). 


Similarly, replacing the potassium acetate employed in the practice of Example 236 by the potassium salt of other fatty acids, such as potassium propionate or potassium butyrate, there are obtained the corresponding fatty acid esters of 14-methyl-A-nor-5β-pregnane-21-ol-3,11,20-trione.

**EXAMPLE 237**

14-methyl-A-nor-5β-pregnane-21-ol-3,11,20-trione (XXXII)

To a solution of 50 mg. of 14-methyl-A-nor-5β-pregnane-21-ol-3,11,20-trione-21-acetate (XXXI) in 20 ml. of methanol is added, with stirring, under nitrogen, 0.2 ml. of 10% oxygen-free potassium carbonate. After 2 hours at room temperature 0.02 ml. of glacial acetic acid is added and after the addition of water, the methanol is removed in vacuo. The mixture is then extracted with chloroform, the chloroform extract washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The resulting crystalline 14-methyl-A-nor-5β-pregnane-21-ol-3,11,20-trione (XXXII) is recrystallized from acetone-hexane.

**EXAMPLE 238**

14-methyl-A-nor-Δ4-pregnene-21-ol-3,11,20-trione (XLIII)


**EXAMPLE 239**

14-methyl-A-nor-Δ5-pregnene-21-ol-3,11,20-trione (LXI)


**EXAMPLE 240**


**EXAMPLE 241**


crystalline material is obtained, which is then separated into the two epimers (i.e., 5a-bromo and 5β-bromo) by crystallization from chloroform-methanol. The first crop amounting to 53 mg. represents the essentially pure 14-methyl-5β-bromo-21-chloro-A-nor-pregnane-3,11,20-trione which on recrystallization from methanol furnishes pure material of the following properties: M.P. 190° with decomposition; [α]D20 +110° (c, 34 in chloroform).

Analysis.—Calculated for C27H41O2BrCl: C, 56.84; H, 6.50. Found: C, 56.75; H, 6.48.

Concentration of the methanolic mother liquor furnishes additional crystalline material (25 mg.) melting at 157° with decomposition which, after recrystallization from methanol, melts at 159–160° and represents the essentially pure 14-methyl-5β-bromo-21-chloro-A-nor-pregnane-3,11,20-trione. It possesses the following properties: M.P. 159–160° with decomposition; [α]D20 +174° (c, 522 in chloroform).

Analysis.—Found: C, 56.77; H, 6.58.


EXAMPLE 257


EXAMPLE 258

EXAMPLE 262


EXAMPLE 263


EXAMPLE 264

14-methyl-5-bromo-A-norpregnane-21-ol-3,11,20-trione 21-acetate (XXXVI and XXXVII)

14-methyl-A-nor-D5-pregnene-21-ol-3,11,20-trione 21-acetate (XVI) (36 mg.) is brominated in 2 ml. of glacial acetic acid with 0.53 ml. of 0.2 molar bromine-sodium acetate solution. The total reaction time is 45 minutes. The crystalline reaction product on recrystallization from methanol furnishes 20 mg. of the 14-methyl-5a-bromo-A-norpregnane-21-ol-3,11,20-trione 21-acetate as the more insoluble product. After recrystallization from methanol, the pure 14-methyl-5a-bromo-A-norpregnane-21-ol-3,11,20-trione 21-acetate is obtained, possessing the following properties: M.P. 185° with decomposition (α)D + 93° (c. 0.85 in chloroform);

λmax 5.75, 5.79 and 5.88 μm

Analysis.—Calcd. for C29H42O3Br: C, 59.10; H, 6.68. Found: C, 59.03; H, 6.76.

Concentration of the methanol mother liquors furnishes 13 mg. of additional material which on recrystallization from methanol yields the essentially pure 14-methyl-5a-bromo-A-norpregnane-21-ol-3,11,20-trione 21-acetate possessing the following properties: M.P. 132-133° with decomposition and resolidification remelting at 175°; (α)D + 88° (c. 0.25 in chloroform);

λmax 5.75, 5.87 and 5.89 μm

EXAMPLE 265


EXAMPLE 266


EXAMPLE 267


EXAMPLE 268


EXAMPLE 269


EXAMPLE 270


EXAMPLE 271


EXAMPLE 272


EXAMPLE 273


EXAMPLE 274


EXAMPLE 275


69 EXAMPLE 276

14-methyl-5-bromo-A-nor-Δ⁵⁺(II)-pregnadiene-21-ol-3,20-dione


EXAMPLE 277

14-methyl-5-bromo-A-nor-Δ⁵⁺(II)-pregnene-21-ol-5,20-dione


EXAMPLE 278

14-methyl-5-bromo-A-nor-Δ⁵⁺(II)-pregnene-21-ol-3,20-dione


EXAMPLE 279

14-methyl-5-bromo-A-norpregnene-21-ol-3,20-dione


EXAMPLE 280

14-methyl-A-nor-Δ⁵⁺-pregnene-3,11,20-trione (XLIV)

A solution of 50 mg. of 14-methyl-5α-bromo-A-norpregnene-3,11,20-trione (XXIX) and 500 mg. of lithium bromide in 5 ml. of dimethylformamide is heated on the steam bath for 2 hours. The mixture is then cooled, diluted with water and extracted with chloroform. The chloroform extract is washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The residual crystals on recrystallization from methanol furnish the pure 14-methyl-A-nor-Δ⁵⁺-pregnene-3,11,20-trione (XLIV) possessing the following properties: M.P. 198°-200°; \( \lambda_{max} \text{nm} \ 5.24 \text{mu} (\varepsilon = 8,300) \).

Similarly, replacing the lithium bromide employed in Example 280 by 200 mg. of lithium chloride, 14-methyl-A-nor-Δ⁵⁺-pregnene-3,11,20-trione (XLIV) is obtained.

EXAMPLE 281

14-methyl-A-nor-Δ⁵⁺-pregnadiene-3,11,20-trione (LXXXV)


EXAMPLE 282

14-methyl-A-nor-Δ⁵⁺-pregnadiene-11β-ol-3,20-dione (CXI)


70 EXAMPLE 283


EXAMPLE 284

14-methyl-A-nor-Δ⁵⁺,Δ⁸⁺(II)-pregnatriene-3,20-dione (CXXIII)


EXAMPLE 285

14-methyl-A-nor-Δ⁵⁺,Δ⁸⁺(II)-pregnatriene-3,20-dione (CXXIII)


EXAMPLE 286

14-methyl-A-nor-Δ⁵⁺-pregnatriene-3,20-dione (LXXXV)


EXAMPLE 287

14-methyl-A-nor-Δ⁵⁺-pregnatriene-3,20-dione (LXXXV)


EXAMPLE 288

14-methyl-21-chloro-A-nor-Δ⁵⁺-pregnene-3,11,20-trione (XLI)

A solution of 14-methyl-5α-bromo-21-chloro-A-norpregnene-3,11,20-trione (XVIII) (2 mg.) and 80 mg. of lithium chloride in 3 ml. of dimethylformamide are heated on the steam bath for 2 hours. The cooled mixture is diluted with chloroform, extracted with water and the resulting chloroform extract dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline residue after recrystallization from methanol furnishes the pure 14-methyl-21-chloro-A-nor-Δ⁵⁺-pregnene-3,11,20-trione (XLI) of the following properties: M.P. 218°-219°; \( \lambda_{max} \text{nm} \ 5.80, 5.91 and 6.044 \text{mu} \ (\varepsilon = 8,700) \).

Analysis.—Calcd. for C₂₃H₅₉Cl₂O₂ (362.87): C, 69.51; H, 7.50. Found: C, 69.52; H, 7.45.


EXAMPLE 289

14-methyl-21-chloro-A-nor-Δ²,5,8-pregna-3,11,20-triene


EXAMPLE 290

14-methyl-21-chloro-A-nor-Δ²,5β-pregna-11β,3β,20-dione (CVIII)


EXAMPLE 291

14-methyl-21-chloro-A-nor-Δ²,5β-pregna-11β,3β,20-dione (CVI)


EXAMPLE 292

14-methyl-21-chloro-A-nor-Δ²,5β,8β-pregna-3,20-dione (CXX)


EXAMPLE 293

14-methyl-21-chloro-A-nor-Δ²,5β,8β-pregna-3,20-dione (CXXVI)


EXAMPLE 294

14-methyl-21-chloro-A-nor-Δ²,5β-pregna-3,20-dione (LXXXII)


EXAMPLE 295


EXAMPLE 296


A solution of 10 mg of 14-methyl-21-chloro-A-nor-Δ²-pregna-3,11,20-triene (XXII), 40 mg of potassium iodide and 40 mg of anhydrous potassium acetate in 10 ml of acetone containing .05 ml of glacial acetic acid per 100 ml of acetone is heated to reflux for 20 hours. The mixture is taken up in water, distill in vacuo until most of the acetone has been removed and the sterol extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline residue on recrystallization from acetonehexane furnishes the pure 14-methyl - A-nor-Δ²-pregna-21,11β,20-triene-3,21,20-dione (LXII) of the following properties: M.P. 160-161°; [α]D P +4° (C, 60); λ max 5.73, 5.80, 5.83, 5.90, 6.05 and 8.05 μ (ε max 240 μ (ε max 9.300)


EXAMPLE 297


EXAMPLE 298


EXAMPLE 299


EXAMPLE 300


EXAMPLE 301


EXAMPLE 302


3,170,919

EXAMPLE 303

14-methyl-A-nor-Δ^5-pregnene-21-ol-3,20-dione 21-acetate (LXXIX)


EXAMPLE 304

14-methyl-A-nor-Δ^5-pregnene-21-ol-3,11,20-trione 21-acetate (XLII)


EXAMPLE 305

14-methyl-A-nor-Δ^5-pregnene-21-ol-3,11,20-trione (XLIII)


EXAMPLE 306

14-methyl-A-nor-Δ^5,Δ^1,Δ^5-pregnadiene-21-ol-3,11,20-trione


EXAMPLE 307

14-methyl-A-nor-Δ^5,Δ^5-pregnadiene-11β,21-diol-3,20-dione (CX)


EXAMPLE 308


EXAMPLE 309

14-methyl-A-nor-Δ^5,Δ^8(11)-pregnatriene-21-ol-3,20-dione (CXXII)


EXAMPLE 310

14-methyl-A-nor-Δ^5,Δ^8(11)-pregnadiene-21-ol-3,20-dione (CXXVIII)


wherein Z is selected from the group consisting of hydrogen, hydroxy, halogen and acetoxy; wherein the acyl is of a hydrocarbon carboxylic acid of less than twelve carbon atoms. R" is hydrogen; R' is selected from the group consisting of hydrogen and hydroxy; and together R" and R' is oxo.
2. A compound selected from the group consisting of steroids having the formulae

3. A compound selected from the group consisting of steroids having the formulae

4. A compound selected from the group consisting of steroids having the formulae

5. A compound selected from the group consisting of steroids having the formulae

6. A compound selected from the group consisting of steroids having the formulae

wherein X is selected from the group consisting of oxo, lower alkylidene and ethylenedioxy; 
R' is hydrogen; R' is selected from the group consisting of hydrogen and hydroxy and together R' and R'' is oxo; and X is selected from the group consisting of oxo and ethylenedioxy.

wherein R'' is hydrogen; R' is selected from the group consisting of hydrogen and hydroxy and together R' and R'' is oxo.

wherein Y is halogen; R'' is hydrogen; R' is selected from the group consisting of hydrogen and hydroxy and together R' and R'' is oxo; and Z is selected from the group consisting of hydrogen, hydroxy, halogen and acyloxy, wherein the acyl is of a hydrocarbon carboxylic acid of less than twelve carbon atoms.

wherein Z' is halogen; R'' is hydrogen; R' is selected from the group consisting of hydrogen and hydroxy and together R' and R'' is oxo; and X is selected from the group consisting of oxo, lower alkylidene and ethylenedioxy.
6. A compound selected from the group consisting of steroids having the formulae

wherein Z′ is halogen; X is selected from the group consisting of oxo and ethylenedioxy; R is hydrogen; R′ is selected from the group consisting of hydrogen and hydroxy; and together R and R′ is oxo.

7. A compound selected from the group consisting of steroids having the formulae

wherein R is selected from the group consisting of hydrogen and lower alkyl; R′ is selected from the group consisting of hydrogen and hydroxy; and together R′ and R″ is oxo.

8. A compound selected from the group consisting of steroids having the formulae

wherein X is selected from the group consisting of oxo, ethylenedioxy and lower alkylidene; R″ is hydrogen; R′ is selected from the group consisting of hydrogen and hydroxy; and together R′ and R″ is oxo; Z′ is selected from the group consisting of oxo and ethylenedioxy; and X is selected from the group consisting of oxo.

9. A compound selected from the group consisting of steroids having the formulae

wherein X is selected from the group consisting of oxo ethylenedioxy; R″ is hydrogen; R′ is selected from the group consisting of hydrogen and hydroxy and together R″ and R′ is oxo; and R is selected from the group consisting of hydrogen and lower alkyl.

10. A compound selected from the group consisting of steroids having the formulae

wherein R is selected from the group consisting of hydrogen and lower alkyl; R′ is selected from the group consisting of hydrogen and hydroxy; and together R′ and R″ is oxo.

11. A compound selected from the group consisting of steroids having the formulae

wherein R is selected from the group consisting of hydrogen and lower alkyl; R″ is an acyl radical of hydrocarbon carboxylic acid of less than twelve carbon atoms; R′ is selected from the group consisting of hydrogen and hydroxy; and R″ is oxo.

12. A compound selected from the group consisting of steroids having the formulae

wherein X is selected from the group consisting of oxo, ethylenedioxy and lower alkylidene; R″ is hydrogen; R′ is selected from the group consisting of hydrogen and hydroxy; and together R′ and R″ is oxo; Z′ is selected from the group consisting of oxo and ethylenedioxy; and X is selected from the group consisting of oxo.
13. A compound selected from the group consisting of methyl 3-isopropylidene-14-methyl-A-nor-5α-androstane-11-one-17β-carboxylic acid.


15. 4,4,14-trimethyl-17β-hydroxymethyl-5α-androstane-3β,11β-diol.


25. A compound selected from the group consisting of methyl-Δ8-pregnane-3,11,20-trione; methyl-Δ8-pregnene-3,11,20-trione; methyl-Δ8-pregnene-3,11,20-trione; and methyl-Δ8-pregnene-3,11,20-trione.

26. A compound selected from the group consisting of methyl-Δ8(11)-pregnadiene-3,20-dione; and methyl-Δ8(11)-pregnadiene-3,20-dione.


No references cited.
It is hereby certified that errors appear in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 5, line 73, for "of" read -- to --; column 10, line 21, for "with" read -- with --; column 14, lines 35 to 45, the formula at the right of the column should appear as shown below instead of as in the patent:

```
COOH

O

W
```

column 19, line 8, for "process" read -- processes --; column 20, line 24, for "(about 2.1 g.)" read -- (about 2.1 g.) --; column 25, line 19, for "analytically" read -- analytically --; line 24, for "C, 71.19;" read -- C, 72.19; --; lines 29 and 30, "-17-carboxylic", in italics, read --17β-carboxylic --, in italics; line 38, for "coling" read -- cooling --; column 26, line 14, for "of" read -- of --; column 28, line 26, for "-3β-17-carboxylic", in italics, read --3β-ol-17-carboxylic --, in italics; line 49, for "-la-androstane-" read --5α-androstane--; column 32, line 32, for "distilled" read -- distilled --; column 35, line 25, for

-A-nor-3(5),9(11)

read

-A-nor-Δ3(5),9(11)

column 38, line 44, for "rotary" read -- rotary --; column 39, line 20, for "cloro-" read -- chloro--; column 40, line 35, for "200 mg. of methyl-A-nor" read -- 200 mg. of methyl 14-methyl-A-nor--; column 45, line 62, for "5β-androstadiene" read -- 5β-androstene --; column 54, line 61, for "-3,2-" read --3,20--; line 67, for "14-methyl-2-bromo-" read --14-methyl-21-bromo--; column 55, line 38, for "$-5β-pregnenes", in italics, read

-5β-pregnane --, in italics; line 55, for "$5β", in italics, read -- Δ1 --, in italics; line 64, for "$-21-fluoro-A-nor-Δ1-5β-pregnenes", in italics, read --21-chloro-A-nor-Δ5-pregnene --, in italics; column 59, line 46, for "311,20-" read -- 3,11,20--; line 52, for "Δ9(11)

read -- Δ9(11) --; column 60, line 67,
for "8.25μ" read -- 8.15μ --; column 61, line 2, for "12-ol-3", in italics, read -- 21-ol-3 --, in italics; line 49, for "41-methyl", in italics, read -- 14-methyl --, in italics; line 59, for "pregnadene", in italics, read -- pregnadiene --, in italics; column 63, line 52, for "pregnenene" read -- pregnene --; column 64, line 56, for "nor-β1" read -- nor-Δ1 --; column 65, line 7, for "5α-bromo" read -- 5α-bromo --; line 23, for "Δ1-pregnenene" read -- Δ1-5β-pregnenene --; column 66, line 8, for "34 in chlf." read -- .34 in chlf. --; line 20, for "522 in chlf." read -- .522 in chlf. --; column 67, line 36, for "C22 31 5 Br" read -- C23 H0 Br --; column 68, line 36, for "5-pregnanene" read 23 31 5

-- 5β-pregnane --; line 63, for "254" read -- 264 --; line 66, for "11β,21-diol-3,20-dione" read -- 21-acetate yields 14-methyl-5-bromo-Δ1-Δ3-pregnenene-11β,21-diol-3,20-dione --; line 74, for "yield" read -- yields --; column 72, line 3, for "distill" read -- distilled --.

Signed and sealed this 10th day of August 1965.

(SEAL)

Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents