Anal. Calcd. for $C_{15}H_{12}N_8O_8$: N, 25.86. Found: N, 25.90.

Table I summarizes the results of this study.

B. From solanesol. Following ozonization of 0.576 g. of the solanesenes prepared from solanesol, the procedure described in A was repeated. The 2,4-dinitrophenylhydrazones of the following carbonyl compounds were isolated: acetone, 0.207 g., m.p. 123.5–124.5°; formaldehyde, 0.048 g., m.p. 166°; levulinaldehyde, 2.82 g., m.p. 237–238°; and methylglyoxal, trace. Infrared absorption studies confirmed the identity of these compounds. Table I summarizes these findings.

Reduction of the ozonide of dihydrosolanesene. Following ozonization of 0.226 g of dihydrosolanesene, the procedure described in A was repeated. The 2,4-dinitrophenylhydrazones of the following carbonyl compounds were isolated: acetone, acetaldehyde, 0.022 g., m.p. 166–167°; levulinaldehyde, 1.23 g., m.p. 235–237°; and formaldehyde, trace. The infrared spectra of these compounds were identical with those of authentic samples. Table I summarizes the results obtained.

Diels-Alder reaction of 1,4-naphthoquinone with the solanesenes. A. From cigarette smoke. A solution of solanesenes (1.00 g.) and 1,4-naphthoquinone (1.00 g.) in 1:1 ethanol-benzene was refluxed for 5 hr. A solution of 300 mg. of potassium hydroxide in 30 ml. of ethanol was added and the resulting mixture was aerated for 6.5 hr. Concentration to dryness, extraction with hexane (100 ml.), followed by concentration of the hexane extract yielded 0.69 g. of a pale yellow oil.

Chromatography using silicic acid yielded 0.59 g. of unchanged solanesenes and 0.049 g. of a substituted anthraquinone whose infrared spectrum was substantially different from those of the anthraquinones derived from neophytadiene or other phytadienes.[3,22] Oxidation of the solanesene-derived anthraquinone was accomplished by solution in 1.5 ml. of sulfuric acid, addition of 0.5 g. of sodium dichromate in 1.5 ml. of water, and heating at 90° for 1 hr. Dilution of the reaction mixture with water followed by extraction with benzene yielded 7 mg. of a carboxylic acid. Chromatography of this material on silicic acid yielded 6 mg. of anthraquinone-2-carboxylic acid, m.p. 285–287°. Crystallization from 4:1 ethanol-water raised the melting point to 288–290°. Melting points of 291–292°,[28,29] 292–293°,[22] and 295–296°[3] have been reported. A mixture melting point with an authentic sample gave no depression. The infrared spectra of this material and that of an authentic sample were identical.

B. From solanesol. Repetition of the reaction sequence described in A using the solanesenes (1.0 g.) prepared from solanesol yielded 11 mg. of anthraquinone-2-carboxylic acid, m.p. 289–291°. A mixture melting point with an authentic sample gave no depression.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CLIV. Alkyl Steroidal D-Ring Lactones[1,2]

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Condensation of 3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone, 3-keto-13α-hydroxy-13,17-oic acid and its lactone with ethyl formate and methoxide afforded respectively the 16-hydroxymethylene, 2-hydroxymethylene, and 2,16-bishydroxymethylene lactones which were catalytically hydrogenated to the 16β-methyl, 2α-methyl, and 2α,16β-dimethyl derivatives. Oxidation of the 16β-methyl-3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone yielded the 3-keto derivative. Conversion of the methyl substituted 3-keto steroidal lactones to Δ^1 and $\Delta^{1,4}$-3-keto lactones is described.

Since Westerfeld's original observation that oxidation of estrone with alkaline hydrogen peroxide afforded a D-ring lactone[3] the peracid oxidation of other 17-keto steroids has been reported[4–8] and the resulting lactones unequivocably established as 13,17-seco steroidal lactones (I) rather than 16,17-seco lactones (II).[8] Biological oxidation of various steroidal substrates has been reported also to produce related D-Ring lactones.[9–11]

In this paper we report the synthesis of a number of C-2 and C-16 methyl-substituted derivatives of testololactone. Our interest in these derivatives stems in part from the reported[12] favorable activity of 2α-methylandrostane-17β-ol-3-one[13] and of 1-

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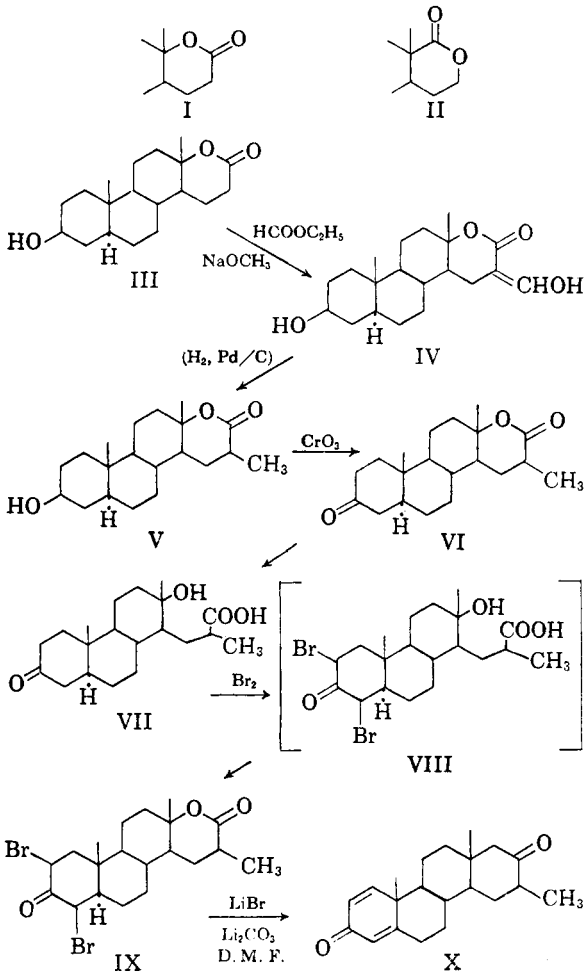

Figure 1

dehydrotestololactone[9,11] in the palliation of cancer of the breast. In particular we hope to establish if a cumulative anti-tumor effect can be obtained by the addition of a 2-methyl group to the testololactone nucleus.

The hydroxymethylene derivatives required as precursors of the mono- and dimethyldihydrotestololactones were obtained in excellent yield by condensation of the appropriate intermediates in benzene solution with ethyl formate and methoxide.[13] Thus 3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone (isoandrololactone) (III), 3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid (XIV) and the lactone of the latter (dihydrotestololactone) (XI) afforded respectively 16-hydroxy-methyleneisoandrololactone (IV), 2-hydroxymethylene-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid (XV), and 3-keto-2,16-bishydroxymethylenedihydrotestololactone (XII). Treatment of the acid with hydrochloric acid resulted in facile ring closure to the lactone (XVI).

Hydrogenation[13] of a suspension of the hydroxymethylene derivatives in methanol or methanol–acetic acid over a palladium carbon catalyst and treatment of the hydrogenation mixtures with alkali followed by relactonization with acid afforded 16β-methylisoandrololactone (V), 2α-methyldihydrotestololactone (XVII), and 2α,16β-dimethyldihydrotestololactone (XIII). The 2α-methyl (equatorial) and 16β-methyl assignments are made on the basis of their stability to alkali treatment, rotatory dispersions, and in the case of the 16β-methyl derivative, on steric factors as well. Chromic acid oxidation of V afforded 16β-methyl dihydrotestololactone (VI).

Addition of a dioxane–carbon tetrachloride solution of bromine to a solution of the acid (VII), prepared by cautious acidification of a cold methanolic potassium hydroxide solution of the lactone (VI), in a dioxane-chloroform mixture gave the crude 2,4-dibromo lactone (IX) resulting from facile lactonization of the intermediary dibromo acid (VIII) under the influence of hydrobromic acid liberated in the reaction. Dehydrobromination of crude IX was effected with a lithium bromide–lithium carbonate suspension in boiling dimethyl formamide. The total product, after treatment with alkali followed by acid, was chromatographed on silica gel to furnish 16β-methyl-$\Delta^{1,4}$-13,17-secoandrostadiene-13α-ol-3-one-17-oic acid lactone [16-β-methyl-1-dehydrotestololactone (X)] with the expected ultraviolet absorption maximum at 242–244 mμ (log ϵ 4.11).[14]

Bromination of the enol acetate (XIX), obtained from 2α-methyldihydrotestololactone (XVII) with isopropenyl acetate, in a mixture of carbon tetrachloride, acetic acid, and sodium acetate[15] afforded the 2-methyl-2-bromo compound (XX) which on dehydrobromination gave 2-methyl-Δ^1-13,17-secoandrostan-13α-ol-3-one-17-oic acid lactone (XXI), λ_{max} 240 mμ. The Δ^1-3-keto structure is assigned on the basis of its method of preparation and infrared and ultraviolet absorption spectra.

Selenium dioxide oxidation of XVII in *t*-butyl alcohol containing a little pyridine afforded 2-methyl-$\Delta^{1,4}$-13,17-secoandrostadiene-13α-ol-3-one-17-oic acid lactone (2-methyl-1-dehydrotestololactone) (XVIII) with ultraviolet maximal absorption at 246 mμ.

EXPERIMENTAL[16]

3β,13α-Dihydroxy-13,17-secoandrostan-17-oic acid lactone (III). This material was prepared from isoandrosterone acetate essentially as described by Levy and Jacobsen[5] with an overall yield from isoandrosterone acetate of 80%. The compound exhibited a melting point of 169–170° (reported[5] 169.7–169.9°); $[\alpha]_D$ −43° (ethanol).

3-Keto-13α-hydroxy-13,17-secoandrostan-17-oic acid lactone (XI). A solution of III, 60.0 g., in 1500 ml. of acetone (distilled from potassium permanganate) at 0° was treated

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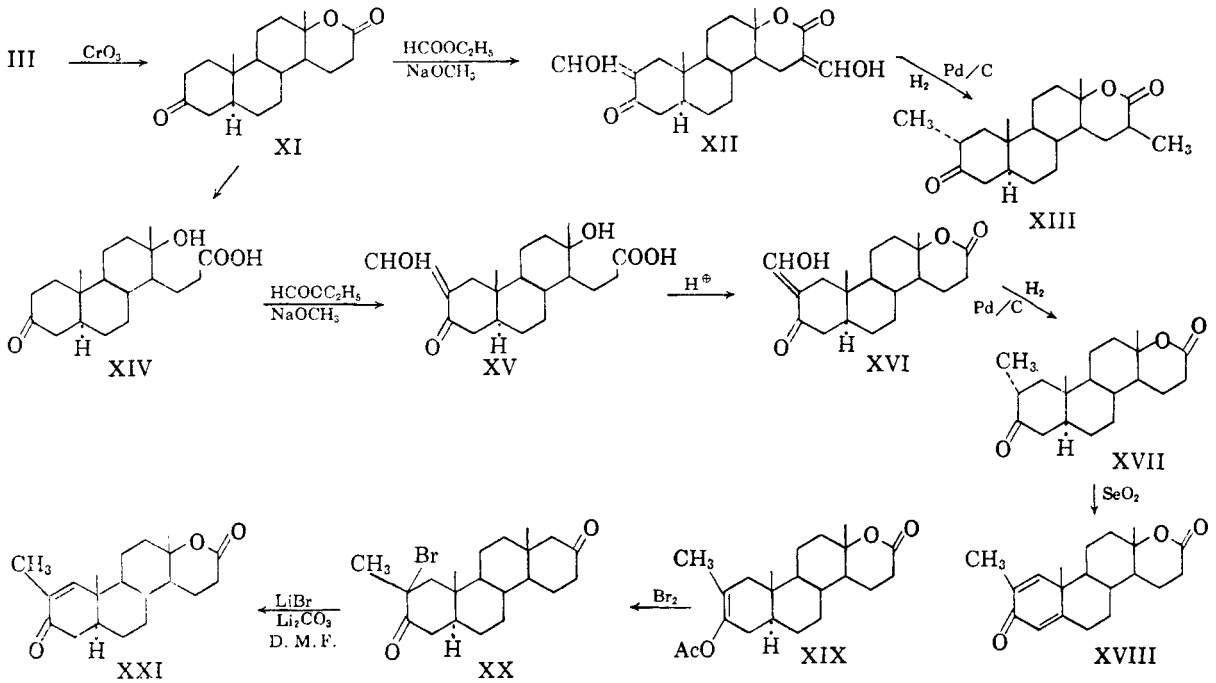

Figure 2

with 66 ml. of 8*N* chromic acid in aqueous sulfuric acid[17] in the usual manner. Methanol (30 ml.) was added, the acetone solution decanted from the green sludge of chromium salts, concentrated to *ca.* 100 ml. and poured into a solution of the sludge of chromium salts in 2.0 l. of cold water. The precipitated product was collected on a filter, washed to neutrality with water and dried. The yield amounted to 53 g., m.p. 156–157° and the product was of sufficient purity for subsequent use. A sample recrystallized from ethyl acetate had m.p. 168–169°; $[\alpha]_D$ −20 (reported[5] m.p. 166–167.7°).

3-Keto-13α-hydroxy-13,17-secoandrostan-17-oic acid (XIV). A suspension of XI in a mixture of 285 ml. of 10% aqueous sodium hydroxide and 2.85 l. of water was heated 1.5 hr. on the steam bath in a nitrogen atmosphere. The hot solution was filtered from a small amount of alkali insoluble material, cooled to 0–5°, and slowly acidified with 300 ml. of 3*N* hydrochloric acid to *p*H 5. The precipitated acid was rapidly filtered by suction, washed to neutrality with cold water, and dried. The crude product amounted to 54 g., m.p. 140–142° raised to 148–149° by one recrystallization from acetone; $[\alpha]_D$ −20°.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38; O, 19.85. Found: C, 70.76; H, 9.26; O, 20.20.

2-Hydroxymethylene-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic lactone (XVI). A mixture of 15.2 g. of XII in 800 ml. of dry thiophene-free benzene, 52 ml. of ethyl formate, and 16 g. of sodium methoxide was stirred at room temperature for 5 hr. The precipitated sodium salt was filtered, washed with benzene (100 ml.) followed by hexane (100 ml.), dried and hydrolyzed by stirring for 1 hr. with 3*N* hydrochloric acid. Filtration and drying afforded XVI, 14.3 g., m.p. 185–190°, raised to 190–195° by one recrystallization from acetone; $[\alpha]_D$ +8°; λ_{max} 282 mμ, (log ε 4.00).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 72.06; H, 8.29; O, 19.45.

2α-Methyl-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid lactone (XVII). A suspension of 13.0 g. of XVI in 80 ml. of methanol was hydrogenated over 4.2 g. of a 10% palladium charcoal catalyst at an initial hydrogen pressure of 30 p.s.i. whence a pressure drop of 6 p.s.i. was observed in 20 min. The crude hydrogenation product was digested with 200 ml. of 10% aqueous potassium hydroxide at steam bath temperature for 1.5 hr., cooled, acidified to *p*H 2 with hydrochloric acid and heated for an additional hour on the steam bath. The cold mixture was filtered and the product washed to neutrality with water affording 11.3 g. of XVII, m.p. 155–160°. Recrystallization from benzene afforded the analytical sample, m.p. 164–167°; $[\alpha]_D$ −19°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.38; H, 9.45.

2-Methyl-$\Delta^{1,4}$-13,17-secoandrostadiene-13α-ol-3-one-17-oic acid lactone (XVIII). A mixture of 1.5 g. of XVII, 90 ml. of anhydrous *t*-butyl alcohol, 0.3 ml. pyridine, and 1.11 g. of selenium dioxide was boiled for 24 hr. under nitrogen when an additional 0.555 g. of selenium dioxide was added. Refluxing was continued for an additional 48 hr. The mixture was cooled to room temperature, filtered through Celite, and evaporated to dryness. The residue was extracted with ether, the extract dried (sodium sulfate) and evaporated to an oil, 0.5 g., which, from acetone-hexane afforded 0.130 g. of XVIII, m.p. 180–190°. An additional 0.100 g. of product, m.p. 214–215° was obtained by absorption on 100 g. of silica and elution with benzene-ether (1:1). A sample recrystallized twice from acetone afforded the analytical sample, m.p. 218–220°; $[\alpha]_D$ −29°; λ_{max} 246 mμ (log ε 4.27).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 76.42; H, 8.24. Found: C, 76.23; H, 8.42.

2,16-Bishydroxymethylene-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid lactone (XII). A mixture of 5.0 g. of XI, 200 ml. of dry thiophene-free benzene, 15 ml. of ethyl formate, and 5.0 g. of sodium methoxide was stirred at room temperature for 5 hr. The precipitated sodium salt was collected, washed with benzene, and the air dried salt hydrolyzed by stirring for 1 hr. with 3*N* hydrochloric acid. The crude product amounted to 5.10 g., m.p. 230–233°. Recrystallization from acetone yielded the analytical sample, m.p. 240–242°, λ_{max} 258–260 mμ (log ε 4.10).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34; O, 22.07. Found: C, 69.81; H, 8.08; O, 22.22.

16-Hydroxymethylene-3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone (IV). A mixture of III (10 g.), 600

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ml. of dry thiophene-free benzene, 40 ml. of ethyl formate, and 10 g. of sodium methoxide was stirred at room temperature for 5 hr. and the product isolated as described for XVI. The yield amounted to 9.2 g., m.p. 290–293°, raised to 292–294° by crystallization from a large volume of methanol; λ_{max} 250–252 mμ (log ε 4.0).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 71.69; H, 8.93; O, 19.14.

16β-Methyl-3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid lactone (V). A suspension of IV (1.0 g.) in glacial acetic acid (130 ml.) and methanol (15 ml.) was hydrogenated over a 10% palladium-charcoal catalyst (1.0 g.) at room temperature for 16 hr. under a hydrogen pressure of 40 p.s.i. The product was isolated as a viscous oil, 0.970 g., which gave a negative reaction with alcoholic ferric chloride. This was heated in a boiling mixture of 30 ml. of methanol and 12 ml. of 10% methanolic potassium hydroxide for 1.5 hr. and evaporated to dryness. The residual oil was taken up in 250 ml. of warm water, filtered, acidified to *p*H 1 with 3*N* hydrochloric acid and stirred at steam bath temperature for 1.5 hr. The product was isolated by ethyl acetate extraction as a partially crystalline solid (0.950 g.). This was absorbed from a benzene solution on 40 g. of silica gel. The fractions eluted with benzene-ether (4:1 and 1:1) were combined and crystallized from acetone-hexane affording pure V, 0.540 g., m.p. 144–146°; $[\alpha]_D$ −54°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 79.96; H, 10.05; O, 14.98. Found: C, 79.73; H, 9.87; O, 15.38.

16β-Methyl-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid lactone (VI). A solution of V (0.500 g.) in 30 ml. of acetone was treated dropwise at 0° with 0.5 ml. of 8*N* chromic acid in aqueous sulfuric acid. Stirring was continued for 15 min., the mixture diluted with water, and the product isolated by extraction with ethyl acetate. Two recrystallizations from ether yielded pure VI, m.p. 190–192°; $[\alpha]_D$ −32°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.07. Found: C, 75.23; H, 9.31; O, 15.20.

16β-Methyl-3-keto-13α-hydroxy-13,17-secoandrostan-17-oic acid (VII). A suspension of VI (0.50 g.) in a mixture of 40 ml. of water and 10 ml. of 10% methanolic potassium hydroxide was stirred on a steam bath under nitrogen until solution was complete (2.5 hr.). Careful acidification of the cold solution with 3*N* hydrochloric acid to *p*H 5 precipitated the acid, which was rapidly filtered, washed to neutrality with water, and dried. Crystallization from acetone afforded 0.410 g. of VII, m.p. 186–188°; $[\alpha]_D$ +24°.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59; O, 19.02. Found: C, 70.99; H, 9.45; O, 18.92.

16β-Methyl-3-keto-13α-hydroxy-13,17-secoandrostan-2,4-dibromo-17-oic acid lactone (IX). To a solution of VII (0.205 g.) in a mixture of 15 ml. of dioxane and 10 ml. of chloroform, 12.2 ml. of a bromine solution (prepared by dissolving 0.90 g. of bromine in 50 ml. of a 1:1 mixture of dioxane and carbon tetrachloride) was added dropwise with stirring in 30 min. The almost colorless reaction mixture was then treated with cold water and extracted with methylene chloride. The organic extract was washed several times with water, dried (sodium sulfate), and evaporated to a yellow oil, 0.230 g., whose infrared spectrum confirmed the absence of unlactonized acid.

Anal. Calcd. for $C_{20}H_{28}Br_2O_3$: Br, 29.80. Found: Br, 28.40.

16β-Methyl-$\Delta^{1,4}$-13,17-secoandrostadiene-13α-ol-3-one-17-oic acid lactone (X). The crude dibromo compound (IX) dissolved in 12 ml. of dimethyl formamide was added dropwise to a boiling suspension of lithium bromide (0.550 g.) and lithium carbonate (0.850 g.) in 10 ml. of dimethyl formamide during 30 min., and the mixture heated under reflux for an additional 4.5 hr. Filtration and evaporation to dryness *in vacuo* afforded a semicrystalline product (200 mg.) which was heated for 1.5 hr. in a boiling mixture of methanol (10 ml.) and 10% methanolic potassium hydroxide (7 ml.). The residue obtained on removal of solvent was taken up in hot water, filtered through a column of Celite (1 g.), strongly acidified (*p*H 1) with 3*N* sulfuric acid, and heated with stirring in a nitrogen atmosphere for 2.5 hr. at steam bath temperature. The product was isolated by extraction of ethyl acetate, taken up in benzene and chromatographed on silica gel (9 g.). Elution with benzene ether (1:1) yielded 0.135 g. of crystalline material, m.p. 216–218° after a single recrystallization from ether; $[\alpha]_D$ −133°; λ_{max} 242–244 mμ (log. ε 4.11).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.27. Found: C, 76.58; H, 8.30; O, 15.00.

Enol acetate of 2α-methyl-3-keto-13α-hydroxy-13,17-secoandrostane-17-oic acid lactone (XIX). A mixture of 1.0 g. of XVII, 65 ml. of isopropenyl acetate, and 200 mg. of *p*-toluenesulfonic acid was heated under reflux for 22 hr. The dark colored oil obtained by evaporation *in vacuo* was taken up in benzene (100 ml.), washed to neutrality with water, dried (sodium sulfate), and evaporated to a crystalline solid. Recrystallization from methanol afforded 0.62 g. of the enol-acetate, m.p. 167–169°, m.p. 169–170° after two further recrystallizations from methanol, $[\alpha]_D$ +14°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.88; H, 8.79; O, 17.52.

2-Methyl-Δ^1-13,17-secoandrostan-13α-ol-3-one-17-oic acid lactone (XXI). Bromine (0.15 ml.) was diluted to 10 ml. with a mixture of acetic acid (100 ml.), carbon tetrachloride (40 ml.), and sodium acetate (2.0 g.). The enol acetate (XIX), 540 mg., was dissolved in 45 ml. of the same mixture and treated dropwise with stirring over a 30-min. period with 5.2 ml. (1.1 equiv.) of the bromine solution. After standing for an additional 10 min., the mixture was diluted with cold water and extracted with methylene chloride. The extract was washed with cold water, 5% sodium bicarbonate, and water to neutrality. The dried (sodium sulfate) extract was evaporated to a crystalline residue which was recrystallized once from methanol affording 220 mg. of the 2-bromo-2-methyl derivative (XX), m.p. 115–117°.

Anal. Calcd. for $C_{20}H_{29}O_3Br$: Br, 20.11. Found: Br, 18.87.

The partially purified bromo derivative (220 mg.) was added dropwise in 30 min. to a suspension of lithium bromide (250 mg.) and lithium carbonate (450 mg.) in 2.5 ml. of boiling dimethyl formamide. The crude product, isolated essentially as described for (X), was absorbed on silica gel and eluted with benzol-ether (3:2) affording 60 mg. of 2-methyl-Δ^1-derivative (XX), m.p. 165–166° unchanged after recrystallizations from acetone, $[\alpha]_D$ −8°, λ_{max} 240 mμ, log ε 4.01.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.00; H, 8.92.

[Added in Proof]

2α,16β-Dimethyl-3-keto-13α-hydroxy-13,17-secoandrostane-17-oic acid, lactone (XIII). Hydrogenation of a suspension of XII, 5.0 g., in a mixture of 190 ml. of ethanol (96%), 9 ml. of water, and 1 ml. of hydrochloric acid over 5.0 g. of a 5% palladium-charcoal catalyst at an initial hydrogen pressure of 30 p.s.i. for 23 hr. afforded an oil which was chromatographed on 150 g. of silic gel. The crystalline fractions eluted with benzene-ether (4:1) were combined and recrystallized from acetone-hexane followed by pure acetone affording 0.840 g. of pure XIII, m.p. 172–176°; $[\alpha]_D$ −34°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.73; H, 9.50; O, 14.86.

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