Benzene–ether (1:1, 1:4), pure ether and ether–methylene chloride (1:1) eluted an additional 1.4 g. of crystals. Acetone–hexane crystallization afforded 1 g. of 2-methylene-17α-methylandrostane-3β,17β-diol (IIa), m.p. 222–225°.

2α,17α-Dimethyltestosterone (VI).—A solution of 0.5 g. of 2-methylene-17α-methyltestosterone (Vd) in 25 ml. of mixture of dry ether–dioxan (4:1) was added rapidly to a stirred solution of lithium (0.2 g.) in liquid ammonia (150 ml.). Ammonium chloride (5 g.) was added immediately to the reaction and the ammonia was permitted to evaporate. The residue was treated with water and the resulting mixture extracted with methylene chloride. The organic extracts were washed with 5% hydrochloric acid and 5% sodium bicarbonate solution and finally with water. Concentration of the sodium sulfate-dried extracts afforded 0.55 g. of oil which was dissolved in hexane–benzene (1:1) and adsorbed on a column of 20 g. of alumina. Elution with mixtures of hexane–benzene (2:3 and 1:2) and with pure benzene provided 0.24 g. of crystals. Crystallization from acetone–hexane gave 0.14 g. of 2α,17α-dimethyltestosterone (VI), m.p. 152–154°, identical in all respects with an authentic sample.[7]

Chromium Trioxide-Pyridine Oxidation of 2-Methylene-17α-methylandrostane-3β,17β-diol (IIa).—A solution of 1 g. of 2-methylene-17α-methylandrostane-3β,17β-diol (IIa) in 20 ml. of pyridine was added to a suspension of chromium trioxide (1 g.) in pyridine (20 ml.). The reaction mixture, after standing for 24 hr., was diluted with ethyl acetate and the solids were removed by filtration through Celite. The filtrate was washed with 5% hydrochloric acid and 5% sodium bicarbonate solution and finally with water. Removal of the solvent afforded 0.66 g. of product which was dissolved in benzene and adsorbed on a column of 25 g. of alumina. The product obtained by elution with ether and ether–acetone (9:1, 4:1 and 1:1) was crystallized from acetone to yield 0.4 g. of dimer, m.p. 215–225°, and raised to 233–238° after 2 additional crystallizations: $[\alpha]_D$ +34°; ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{42}H_{64}O_4$: C, 79.70; H, 10.19. Found: C, 80.38; H, 10.32.

Steroids. CCX.[1] Ring A Modified Hormone Analogs. Part VI. Δ²- and 2-Formyl-Δ²-17β-ol-17α-propionic Acid Spirolactones

PIERRE CRABBÉ, J. REVILLA,[2] AND A. BOWERS

Research Laboratories, Syntex, S.A., Apartado 2679, Mexico, D.F., Mexico

Received July 30, 1962

The preparation of Δ²-androstene-17β-ol-17α-propionic acid lactone (VII) and 2-formyl-Δ²-androstene-17β-ol-17α-propionic acid lactone (X) is described.

Some pharmacological agents are capable of evoking renal modulation of electrolyte and water balance. Among these drugs, the diuretics, the action of which is dependent upon a functionally active kidney, act upon this organ in increasing the flow of urine.[3]

The synthesis of steroidal aldosterone antagonists has recently been described.[4-9]

These compounds, which are 17-spirolactones of the androstane series, are active biologically in that they are antagonists of the renal tubular action of aldosterone.[10a] Recently, anti-inflammatory properties also have been found for these 17-spirolactones.[10b]

The original studied[4,5] of the Searle group with 3-(Δ⁴-androstene-17β-ol-3-one-17α-yl)-propionic acid γ-lactone (Ia) and its 19-nor analog Ib were extended to various substituted homologs in attempts to increase their oral and aldosterone-blocking activities. The effect of methyl substitution at C-2, C-4, C-6, C-7 and C-16[8] and the introduction of Δ¹- and Δ⁶-double bonds[6] was examined. One of the more successful modifications of the Δ⁴-3-ketone 17-spirolactone I was the corresponding 7α-acetylthio analog.[6] All of these compounds however had the "classical" Δ⁴-3-keto chromophore in ring A.

Following the general considerations developed in the first paper of this series,[11] it was of interest to prepare some "non-classical" 3-desoxy-17-spirolactones in which the electron density requirements of ring A were met by a Δ²-double bond[11] or a 2-formyl-Δ²-grouping.[12]

A suitable starting material for the preparation of these "non-classical" spirolactones VII and X, was androstane-3β-ol-17-one (II),[13] which on reaction with ethynylmagnesium bromide[14] readily afforded 17α-ethynylandrostane-3β,17β-diol (IIIa).[15] Attempts to prepare the carboxylic acid IV by an exchange reaction with methymagnesium bromide and the 17α-ethynyl compound IIIa, then carboxylation, were unsuccessful, presumably due to the immediate precipitation of an insoluble complex formed by the interaction of the methylmagnesium bromide with the 3β-hydroxyl group of IIIa. This problem was overcome by conversion of the 3β-alcohol IIIa into its 3-(2′-tetrahydropyranyl)-ether IIIb.[16] The latter IIIb smoothly

(1) Steroids CCIX and Part V, J. A. Edwards, M. C. Calzada and A. Bowers, *J. Med. Chem.*, **6**, 178 (1963).

(2) This work constitutes part of the undergraduate thesis submitted by J. R. to the University of Mexico.

(3) For a discussion of the functions of the kidney and the effects of diuretics on water balance, *cf.* "The Pharmacologic Principles of Medical Practice," J. C. Krantz and C. J. Carr, The Williams and Wilkins Co., Baltimore, Md., 1961, Part VIII, Chapter 51, p. 1206.

(4) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957); (b) C. M. Kagawa, J. A. Cella and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(5) J. A. Cella, E. A. Brown and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(6) J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959).

(7) E. A. Brown, R. D. Muir and J. A. Cella, *ibid.*, **25**, 96 (1960).

(8) N. W. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted and P. B. Sollman, *ibid.*, **26**, 3077 (1961).

(9) L. J. Chinn, H. L. Dryden and R. R. Burtner, *ibid.*, **26**, 3910 (1961); L. J. Chinn, *ibid.*, **27**, 1741 (1962).

(10) (a) For a recent review see: K. H. Beyer and J. A. Baer, *Pharm. Revs.*, **13**, 517 (1961), and references cited therein; (b) E. Bajusz and G. Jasmin, *Rec. Can. Biol.*, **20**, 829 (1961).

(11) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(12) (a) J. C. Orr, O. Halpern and A. Bowers *ibid.*, **5**, 409 (1962); (b) J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, I. Delfin, A. de la Roz, A. M. Ruiz and A. Bowers, *ibid.*, **6**, 166 (1963).

(13) See *inter alia:* (a) L. Ruzicka, M. W. Goldberg and H. Brüngger, *Helv. Chim. Acta*, **17**, 1395 (1934); (b) J. von Euw and T. Reichstein, *ibid.*, **25**, 988 (1942); (c) D. H. R. Barton, *J. Chem. Soc.*, 1116 (1946), and references therein.

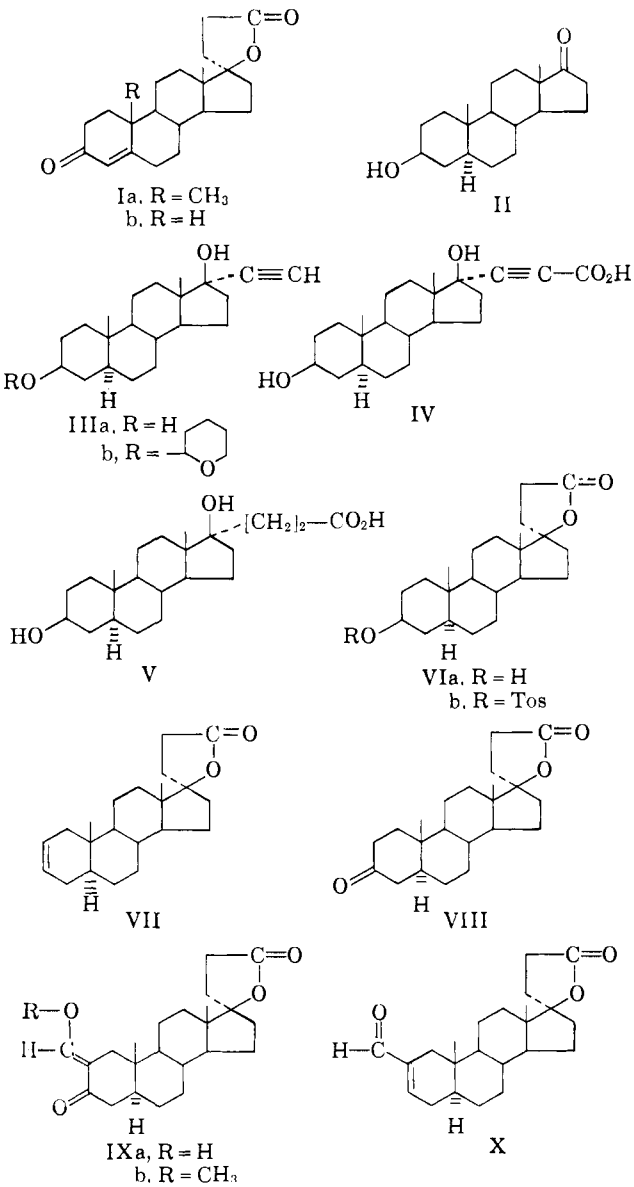
(14) L. Skattebøl, E. R. H. Jones and M. C. Whiting, *Org. Syn.*, **39**, 56 (1959).

(15) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) J. Kathol, W. Lögemann and A. Serini, *Naturwiss.*, **25**, 682 (1937).

underwent the Grignard exchange reaction, then reaction with carbon dioxide to afford the corresponding 17α-propiolic acid IV. Hydrogenation of the acetylenic bond in methanol in the presence of a 5% palladium-on-charcoal catalyst led to the saturated acid V, which in the presence of a trace of acid, cyclized to the γ-lactone VIa.

The corresponding 3-tosylate VIb smoothly underwent elimination upon heating under reflux in collidine to furnish the Δ^2-androstene-17-spirolactone VII.

Oxidation of the propionic acid lactone VIa with chromic acid in acetone–dilute sulfuric acid[17] gave the corresponding 3-ketone VIII, the physical constants of which are in good agreement with those published by the Searle group.[5] Condensation of this ketolactone VIII with ethyl formate led to attack of the lactone ring as well as at C-2. Exclusive condensation at C-2 was effected by carrying out the reaction with ethyl formate with a suspension of the sodium salt of the steroid-17α-propionic acid in benzene–tetrahydrofuran.[18] Treatment of this product with tartaric acid gave the 2-hydroxymethylene analog IXa of the 3-keto-17-spirolactone. Conversion of this substance IXa into the 2-formyl-Δ^2-spirolactone X then followed essentially the procedure outlined earlier from our Laboratories.[12] Formation of the methyl ether IXb by reaction with methanol containing a trace of perchloric acid was followed by reduction of the 3-keto group with sodium borohydride and treatment of the resulting β-hydroxy-vinyl ether with acid to effect a concerted hydrolysis and elimination reaction, leading to the 2-formyl-Δ^2-17-spirolactone X.



Experimental[19]

17α-Ethynylandrostane-3β,17β-diol-3-(2′-tetrahydropyranyl)-ether (IIIb).—17αEthynylandrostane-3β,17β-diol[15] (IIIa) was prepared from androstane-3β-ol-17-one[13] (II) by a Grignard reaction with ethynylmagnesium bromide,[14] and working up in the normal manner.

17α-Ethynylandrostane-3β,17β-diol (IIIa) (25 g.) m.p. 264–266°; $[\alpha]_D$ −41° (*c*, 1.1; CH_3OH) were dissolved in 1380 ml. of anhydrous benzene after which about 400 ml. of benzene was distilled off under vacuum. The remaining solution was cooled to room temperature. To this solution was added 56 ml. of redistilled dihydropyran and 1.1 g. of recrystallized *p*-toluenesulfonic acid monohydrate. After being kept 1 hr. at room temperature and then 13 hr. at 5°[16] water was added and the organic layer was washed first with 10% sodium carbonate solution, and then with water to neutrality. After being dried over anhydrous sodium sulfate, the organic layer was concentrated under vacuum. The crude product, m.p. 175–176°, (28.4 g.) was recrystallized from methylene chloride–methanol to afford an analytical sample of 17α-ethynylandrostane-3β,17β-diol-3-(2′-tetrahydropyranyl)-ether (IIIb), m.p. 182–184°, $[\alpha]_D$ −86° (*c*, 1); λ_{max}^{KBr} 3.0, 3.13 and 4.36 μ.

Anal. Calcd. for $C_{26}H_{40}O_3 \cdot 0.5\ CH_3OH$: C, 76.45; H, 10.16; O, 13.39. Found: C, 76.82; H, 9.87; O, 13.31.

Androstane-3β,17β-diol-17α-propiolic Acid (IV).—To a boiling solution of 72 ml. of methylmagnesium bromide in ether (3 *M*) in 190 ml. of anhydrous tetrahydrofuran there was added a solution of 12 g. of the above ether IIb in 60 ml.[14] of anhydrous tetrahydrofuran. When the addition was complete, a further 24 ml. of ethereal methylmagnesium bromide was added. The mixture was allowed to reflux for 16 hr. A further 24 ml. of Grignard reagent then was added and reflux continued for 24 hours. The reaction mixture was cooled to room temperature and then poured into a dewar flask where it was mixed with Dry Ice and allowed to stand for 65 hr. The mixture was then poured into 1.5 l. of 2 *N* sulfuric acid and extracted with ethyl acetate. The organic layer was washed several times with a saturated aqueous solution of sodium bicarbonate. To the bicarbonate extracts 30% aqueous hydrochloric acid was added carefully until acidity was achieved.

The acid IV which precipitated was filtered off, washed with water and dried under vacuum, to give the crude product: m.p. 240–250° (7.5 g.). Further recrystallizations from methanol–water afforded the pure sample of androstane-3β,17β-diol-17α-propiolic acid (IV), m.p. 248–250° (dec.); $[\alpha]_D$ −46° (*c*, 0.4; CH_3OH); λ_{max}^{EtOH} 209 mμ[20] (log ε 3.74); λ_{max}^{KBr} 2.81, 5.85 μ.

(16) (a) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950); (b) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *ibid.*, 1190 (1951); (c) A. C. Ott, M. F. Murray and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952); (d) F. Sondheimer, N. Stjernström and D. Rosenthal, *J. Org. Chem.*, **24**, 1280 (1959).

(17) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(18) L. H. Knox, R. Villotti, F. A. Kinel and H. J. Ringold, *ibid.*, **26**, 501 (1961).

(19) Microanalyses were carried out by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany, or by Midwest Microlab, Inc., Forest Lane, Indianapolis 20, Ind., U.S.A. Except where otherwise stated rotations were taken in chloroform solution. Melting points were determined in capillary tubes with a "Mel-Temp" apparatus and are uncorrected. Infrared spectra were taken with a Perkin–Elmer Model 21, equipped with a NaCl prism. Ultraviolet absorption spectra are for 95% ethanol solutions and were measured with a Beckman Spectrophotometer, Model D.U. Alumina was prepared as described in ref. 11, footnote 42.

(20) This ultraviolet spectrum was obtained with a Beckman spectrophotometer, Model D.K. 2.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.24; H, 8.86; O, 17.90.

Androstane-3β,17β-diol-17α-propionic Acid (V) and Androstane-3β,17β-diol-17α-propionic Acid Lactone (VIa).—A solution of 500 mg. of the propiolic acid IV in 20 ml. of methanol was stirred under a hydrogen atmosphere in the presence of 0.3 g. of 5% palladium on carbon until two equivalents of hydrogen had been absorbed. Stirring was discontinued and the catalyst filtered off. Methanol was removed by vacuum distillation to afford the crude acid V, m.p. 195–196° (450 mg.). Further recrystallization from ethanol–water gave a pure sample of androstane-3β,17β-diol-17α-propionic acid (V); m.p. 198–200°; $[\alpha]_D$ −2° (*c*, 0.6; CH_3OH); λ_{max}^{KBr} 3.1, 5.92 μ.

When this acid V was recrystallized from methanol containing traces of hydrochloric acid the corresponding lactone VIa was obtained. By further recrystallization from methylene chloride–methanol there was obtained an analytical sample of androstane-3β,17β-diol-17α-propionic acid lactone (VIa): silky plates, m.p. 201.5–202°; $[\alpha]_D$ −19° (*c*, 1); λ_{max}^{KBr} 2.86, 5.68 μ. Cella, *et al.*, reported[5]: m.p. 199–201°, $[\alpha]_D$ −20°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.42; H, 9.77; O, 13.91.

Androstane-3β,17β-diol-17α-propionic Acid 3-Tosylate (VIb). To a solution of 1.5 g. of the lactone VIa in 40 ml. of anhydrous pyridine was added 3 g. of recrystallized *p*-toluenesulfonyl chloride. The mixture then was allowed to stand overnight at room temperature, after which water was added and the mixture extracted with methylene chloride. The organic layer was first washed with 10% aqueous hydrochloric acid, then with 5% sodium bicarbonate solution and finally with water. After being dried over anhydrous sodium sulfate, the solvent was evaporated under vacuum, giving 1.5 g. of the crude tosylate VIb, m.p. 143–145°. Further crystallization from acetone–hexane gave pure androstane-3β,17β-diol-17α-propionic acid 3-tosylate (VIb), as needles, m.p. 151–152° (dec.); $[\alpha]_D$ −22° (*c*, 1); λ_{max}^{EtOH} 226 mμ (log ε 4.11), 256 mμ (log ε 2.68), 262 mμ (log ε 2.77), 267 mμ (log ε 2.72), 274 mμ (log ε 2.62); λ_{max}^{KBr} 5.65, 7.5 and 8.6 μ.

Anal. Calcd. for $C_{29}H_{40}O_5S$: C, 69.57; H, 8.05; S, 6.40. Found: C, 69.80; H, 8.19; S, 5.77.

Δ²-Androstene-17β-ol-17α-propionic Acid Lactone (VII).—Androstene-3β,17β-ol-17α-propionic acid 3-tosylate (VIb) 1.5 g. was dissolved in 120 ml. of freshly distilled dry collidine and the mixture refluxed for 2 hr. under nitrogen. After cooling, water was added and then ethyl acetate. The organic phase was washed several times with 10% hydrochloric acid, and with water to neutrality, dried over anhydrous sodium sulfate and concentrated under vacuum to give an amorphous material. This compound was further purified by chromatography over alumina. Elution of the column with hexane–benzene (9:1) afforded 950 mg. of crystalline Δ²-compound VII, m.p. 130–132°. Further recrystallization from acetone–hexane gave pure Δ²-androstene-17β-ol-17α-propionic acid lactone (VII): long needles, m.p. 134–136°; $[\alpha]_D$ +17° (*c*, 0.8).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.42; H, 9.72.

Androstane-17β-ol-3-one-17α-propionic Acid Lactone (VIII).—A solution of 1.69 g. of the lactone VIa in 60 ml. of acetone (twice distilled over potassium permanganate) was cooled to 0° and 1.5 ml. of 8 *N* chromic acid–sulfuric acid solution[15] was added dropwise with stirring. When the addition was complete stirring was continued for two minutes. To this mixture 5% sodium bicarbonate solution was added to pH 8. Ethyl acetate extracts were washed with water to neutrality, and then dried over anhydrous sodium sulfate. The ethyl acetate was removed by vacuum distillation to yield 1.5 g. of crude keto-lactone VIII m.p. 170–175°. Purification of this compound by chromatography followed by recrystallization from acetone–hexane gave the pure sample of androstane-17β-ol-3-one-17α-propionic acid lactone (VIII): m.p. 177–178°, $[\alpha]_D$ +5° (*c*, 0.8). Reported by Cella, *et al.*[5]; m.p. 178–179°; $[\alpha]_D$ +5° ($CHCl_3$); λ_{max}^{KBr} 5.67 and 5.8 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.94. Found: C, 76.47; H, 9.26; O, 14.27.

2-Hydroxymethyleneandrostane-17β-ol-3-one-17α-propionic Acid Lactone (IXa).—A mixture of 1.2 g. of androstane-17β-ol-3-one-17α-propionic acid lactone (VIII), 150 ml. of methanol and 70 ml. of 20% aqueous sodium hydroxide was boiled under reflux for 1 hr. Methanol then was removed by distillation and the sodium salt of the 17α-propionic acid which precipitated out was filtered off and dried under high vacuum. From a suspension of this salt in 200 ml. of anhydrous benzene, 50 ml. of benzene was distilled to remove moisture. The remaining suspension was cooled to room temperature and 3.8 g. of sodium methoxide added, then 7.5 ml. of ethyl formate and 25 ml. of anhydrous tetrahydrofuran. This mixture was stirred under nitrogen for 16 hr. at room temperature. Water then was added and the organic layer, which separated, was discarded. To the aqueous layer was added 35% aqueous tartaric acid to pH 4. The precipitate was collected, washed with water and dried under vacuum to afford 1.2 g. of the crude hydroxymethylene derivative IXa, m.p. 160–163°; λ_{max}^{EtOH} 282–284 mμ (log ε 3.88). The analytical sample of 2-hydroxymethyleneandrostane-17β-ol-3-one-17α-propionic acid lactone (IXa) was obtained by sublimation (170–190°, 0.5 mm.), m.p. 173–176°; $[\alpha]_D$ +22° (*c*, 1.05; C_2H_5OH); λ_{max}^{EtOH} 282 mμ (log ε 3.90); λ_{max}^{KBr} 3.0, 5.68, 6.12 and 6.33 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 73.99; H, 8.69; O, 17.32.

2-Hydroxymethyleneandrostane-17β-ol-3-one-17α-propionic Acid Lactone-2-methyl Ether (IXb).—A suspension of 2 g. of the hydroxymethylene derivative (IXa) in 10 ml. of methanol was treated with two drops of 70% perchloric acid. The mixture was stirred until all the compound had dissolved and then kept at room temperature, 0.5 hr. The methyl ether which precipitated was collected, washed with methanol and dried, affording 1.75 g. of crude ether IXb, m.p. 180–210°. Further recrystallization from methanol gave a pure sample of 2-hydroxymethyleneandrostane-17β-ol-3-one-17α-propionic acid lactone-2-methyl ether (IXb) as long needles, m.p. 248–249°; $[\alpha]_D$ −3° (*c*, 1); λ_{max}^{EtOH} 276 mμ (log ε 4.07); λ_{max}^{KBr} 5.65, 5.97 and 6.3 μ.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.59; H, 8.93; O, 16.80.

2-Formyl-Δ²-androstene-17β-ol-17α-propionic Acid Lactone (X).—To a solution of 330 mg. of ether IXb in 60 ml. of ethanol was added 10 ml. of a 5% ethanolic sodium borohydride solution. The mixture then was left at room temperature until no ultraviolet absorption at 276 mμ could be detected (around 15 minutes). Water then was added and 10% hydrochloric acid solution to regenerate the free 17α-acid and reclose the lactone ring. Ethyl acetate extracts were washed with water, dried (Na_2SO_4) and evaporated *in vacuo*, to furnish an amorphous material showing infrared absorption for the γ-lactone (5.65 μ) and only weak absorption for the 2-formyl-Δ²-system (5.95 and 6.08 μ).

This crude 2-hydroxymethyleneandrostane-3,17β-diol-17α-propionic acid lactone-2-methyl ether was not purified further but was dissolved immediately in methanol containing a few drops of concentrated hydrochloric acid. The formation of the 2-formyl-Δ²-system was followed by ultraviolet absorption at 232 mμ and the reaction was quenched when no increase of the ε value could be detected (around 15 minutes). Water then was added and the product extracted with ethyl acetate. The organic phase was washed with water until neutral and dried over anhydrous sodium sulfate. Removal of solvent under vacuum led to a solid, m.p. 160–163°; λ_{max}^{EtOH} 232 mμ (log ε 3.75) which was purified by chromatography over alumina. Elution of the column with hexane–benzene (1:1) afforded 2-formyl-Δ²-androstene-17β-ol-17α-propionic acid lactone (X), which by recrystallization from acetone–hexane gave the analytical sample m.p. 193–195°; $[\alpha]_D$ +45° (*c*, 1); λ_{max}^{EtOH} 232 mμ (log ε 4.10); λ_{max}^{KBr} 3.71, 5.67, 5.97 and 6.1 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 77.49; H, 9.05. Found: C, 77.63; H, 9.29.