drops of glacial acetic acid and 50 mg. of zinc dust was added. After 1 min. of stirring the tetrabromide dissolved. Occasional stirring was provided during an additional 15 min. period. Ether was added to the solution and this was decanted from the zinc. The ether solution was washed with water and dried. Crystallization of the residue left after evaporation of the ether gave 30 mg. of the acetate, m.p. 129–131°. An additional crystallization sharpened the melting point to 130.5–131°. The infrared spectrum of this material was identical in every minute detail to that of 29-isofucosteryl acetate. No change had occurred in the structure of the steryl acetate during the bromination and debromination steps.

Ozonolysis of 29-isofucosteryl acetate. A solution of 260 mg. of the acetate in 50 ml. of cold purified glacial acetic acid was subjected to a stream of ozone (6%) for 5 min. Zinc dust was added to decompose the ozonide. This was shaken and then filtered. The water from a gas scrubber (25 ml.) used in the ozonolysis train was added to the acetic acid solution and the material was distilled until approximately 25 ml. of distillate was collected.

The distillate was poured into a solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The derivative precipitated immediately. After filtration, the material was dissolved in chloroform and chromatographed on a column of Bentonite:Celite 545 (3:1).[19] The derivative was eluted with chloroform-ethanol (10:1). Crystallization from ethanol gave the 2,4-dinitrophenylhydrazone of acetaldehyde, m.p. 160–162°. This was identical to an authentic sample (mixed melting point, infrared spectrum, paper chromatogram).

Isolation of fucosterol from Fucus vesciculosus. The ether extract of the air-dried material was saponified to give the pure sterol after several crystallizations from methanol, m.p. 122–123°; λ_{max} 11.90, 12.17 and 12.50 μ. The sterol was acetylated to give the acetate. Crystallization from methanol gave the pure acetate, m.p. 119–120°; λ_{max} 5.77, 6.00, 8.02, 11.92, 12.14, 12.19 (sh) and 12.47 μ. Addition of bromine gave the acetate tetrabromide, m.p. 131–133° dec. Debromination with zinc and acetic acid gave back fucosteryl acetate.

Wittig reaction of methyl isopropyl ketone with triphenylphosphonium ethylidene. To a heavy slurry of 13.15 g. (35.4 mmol.) of triphenylethylphosphonium bromide in 15 ml. of absolute ether was added 25.9 ml. of 1.3*N* butyllithium solution (33.7 mmol.). The solution was stirred for 1 hr. to give a red solution with the suspended excess salt. The solution was cooled to 0° and 3.62 ml. of dry redistilled methyl isopropyl ketone (2.90 g., 33.7 mmol.) was added and the heavy precipitate stirred for 1 hr. The pressure flask was then capped and heated to 65° for 3 hr. in an oil bath.

After cooling, the flask was opened and a column attached and as much ether distilled (bath 70°) as possible. The pressure was reduced and the distillate collected in a Dry Ice-cooled receiver. This material was distilled and gave 0.45 g. of olefin with a considerable loss due to hold-up. The following physical constants were obtained after another vacuum distillation; b.p. 85–88° (microdetermination); n_D^{28} 1.4163; λ_{max}^{neat} 6.00, 7.25, 7.30, 7.37, 12.18–12.27 (sh) and 12.33μ; reported for 3,4-dimethyl-2-pentene (*cis* or *trans* not specified) b.p. 86.2–86.4°, n_D^{25} 1.4052[20]; b.p. 85–89°, n_D^{27} 1.4100[21]; b.p. 91°, n_D^{21} 1.4135[22]; b.p. 87°, n_D^{21} 1.404.[23]

Gas chromatography of a sample of the olefin in a four meter column and operated at 85° showed an isomer ratio of 9:1.

Acknowledgment. The author is indebted to Professor Werner Bergmann for his advice, encouragement and suggestions during the course of this work.

NEW HAVEN, CONN.

(19) J. W. White, *Anal. Chem.*, **20**, 725 (1948); J. A. Elvidge and M. Whalley, *Chem. and Ind.* (London), 589 (1955).

(20) F. J. Soday and C. E. Boord, *J. Am. Chem. Soc.*, **55**, 3293 (1933).

(21) I. N. Narsarov, *Ber.*, **70**, 617 (1937).

(22) A. Guillemonat, *Ann. Chim.*, **11**, 143 (1939).

(23) Selective Values of Properties of Hydrocarbons, National Bureau of Standards, Circular 0461, November 1947, Washington, p. 49.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

Steroidal Aldosterone Blockers. III[1,2]

EDWARD A. BROWN, ROBERT D. MUIR, AND JOHN A. CELLA

Received July 13, 1959

The syntheses and biological activities of several new steroidal 17-spirolactones are presented. Oxygenation of position 11 in the steroid nucleus produces some increase of aldosterone blocking activity and this activity is further enhanced by the additional introduction of 9-α-fluoro substituent.

Earlier articles[1] in this series reported on a number of steroidal 17-spirolactones bearing modifications in the lactone and 3-oxo-4-ene systems; nuclear unsaturation and acylthio substituents were also introduced. This article reports on a number of oxygenated steroidal 17-spirolactones and related derivatives. The basic structures subjected to modification in this work were those of 3-(3-oxo-17β-hydroxy-4-androsten-17-α-yl)propanoic acid lactone (Ia) and its 19-nor analog (Ib).

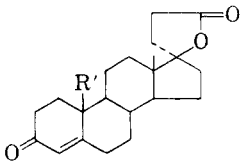
Monohydroxy derivatives of Ia and Ib were prepared both by adrenal perfusion[3] and by fermentation with a species of *Rhizopus*. Perfusion has been shown to give predominantly 11β-hydroxylation.[4] The products of perfusion, IIe and IIb, were oxi-

(1) Paper II, J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959).

(2) Presented in part before the Division of Medicinal Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

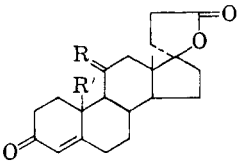
(3) These perfusions were carried out at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., by Mr. Austin Fish.

dized to the corresponding ketones, IId and IIa, which showed hypsochromic shifts in ultraviolet absorption maxima when compared to the hydroxy compounds. This is a characteristic effect of a ketone at C-11 on the absorption of the 3-keto-4-ene system.[5] The compounds IIf and IIc, obtained from fermentation of Ia and Ib with a species of *Rhizopus*, were oxidized to yield the identical ketones obtained by oxidizing IIe and IIb. The ultraviolet absorption spectra of IIc and IIf showed no significant changes on standing at room temperature in 0.1*N* methanolic potassium hydroxide twenty four hours, indicating that the hydroxyl groups could not be in the C-2, C-6, or C-7 positions.[6] On the basis of the foregoing evidence, we have assigned the 11β- and the 11α-hydroxyl structures to the perfusion and fermentation products respectively.



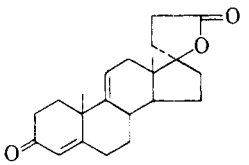
I

a. R′ = CH_3
b. R′ = H

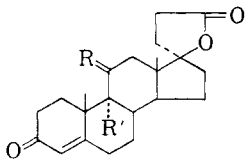


II

a. R = O, R′ = H
b. R =  , R′ = H
c. R =  , R′ = H
d. R = O, R′ = CH_3
e. R =  , R′ = CH_3
f. R =  , R′ = CH_3
g. R =  , R′ = CH_3

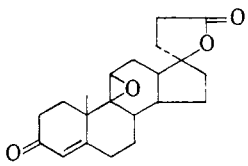


III

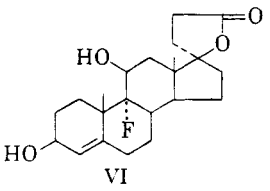


IV

a. R =  , R′ = Br
b. R =  , R′ = F
c. R = O, R′ = F



V



VI

The remarkable biological activities of the 9α-halo corticoids made it of interest to prepare 9α-fluoro-11β-hydroxy-17-spirolactone derivatives. The 9α-fluoro-11β-hydroxy derivative (IVb) was prepared from the 11α-hydroxyl compound (IIf) by the method of Fried and Sabo[7] involving conversion of the 11α-mesylate (IIg) to the 9(11)-ene (III). Hypobromous acid addition gave the 9,11-bromohydrin (IVa) which on treatment with potassium acetate in absolute ethanol gave the 9β,11β-epoxide (V). The fluorohydrin was then obtained by addition of hydrogen fluoride to this epoxy compound. In order to increase its solubility the 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) was reduced to the 3β-hydroxy-4-ene compound (VI) with sodium borohydride in methanol. Assignment of the 3β-configuration is based on the work of previous investigators[8,9] who have noted that the 3β-hydroxyl is the preferred product in the sodium borohydride reduction of Δ^4-cholestenone. It also appeared desirable to prepare the 9α-fluoro-11-keto compound (IVc) and this was accomplished by oxidation of IVb with pyridine–chromic acid complex.

The biological studies, reported in Table I, were conducted by Dr. C. M. Kagawa of these laboratories. It has been demonstrated that a definite and proportional relationship exits between the blocking effects of typical steroidal spirolactones when tested on rats treated with aldosterone and with desoxycorticosterone acetate (DOCA).[10] The more available DOCA was employed as the sodium retaining agent throughout this work.

TABLE I

DESOXYCORTICOSTERONE ACETATE BLOCKING POTENCIES

Compound	M.E.D.[a] Oral	M.E.D.[a] Subcutaneous
Ia	19.2	0.26
Ib	2.2	0.07
IIa	>0.6	<0.6
IIb	0.48	0.17
IIc		>2.4
IIe		1.1
IIf		>2.4
IIg		>1.2
III	>1.2	0.52
IVa		>1.2
IVb	>0.5	0.22
IVc	0.2	0.05
V		>1.2
VI	0.39	0.14

[a] M.E.D. is the medium effective dose (total mg./rat) which when used with 12 μg. of desoxycorticosterone acetate in adrenalectomized rats produces the same urinary sodium-potassium ratio as that which results from the use of 6 μg. of DOCA alone.

(4) O. Hechter, R. P. Jacobsen, R. Jeanloz, H. Levy, C. W. Marshall, G. Pincus, and V. Schenker, *J. Am. Chem. Soc.*, **71**, 3261 (1949) and *Arch. Biochem.*, **25**, 457 (1950).
(5) L. Dorfman, *Chem. Rev.*, **53**, 72 (1953).
(6) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1954).
(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).
(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).
(9) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).
(10) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1953).

An increase in oral activity is noted with introduction of the 11β-hydroxyl function. The most active compound is 3-(3,11-dioxo-9α-fluoro-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IVc).

EXPERIMENTAL

The microanalyses and optical determinations were carried out by Dr. Robert T. Dillon and his associates of these laboratories.

General procedures are reported for adrenal perfusion and microbiological oxidation techniques. Reference is made to them when they were used for specific preparations.

Melting points were determined on a Fisher-Johns block and are reported uncorrected. Ultraviolet spectra were determined in methanol. Optical rotations were measured in chloroform except as otherwise noted.

Procedure A: adrenal perfusion.[3] The perfusion medium is prepared by mixing 7 volumes of citrated whole beef blood with 5 volumes of "modified" (calcium chloride omitted) Tyrode Solution and subjecting the resultant mixture to the action of a stream of oxygen during a 2.5-hr. period. A solution of 1 g. of the steroid in 40 ml. of propylene glycol is added to 250 ml. of this medium and the mixture is then perfused at 36–37.5° through 8 beef adrenals (av. wt. 17.9 g. each) prepared according to the technique of Hechter and co-workers.[11] During the course of perfusion, oxygen is continuously bubbled through the medium. After approximately 3 hr., in the course of which 6 passes of the medium through the glands are completed, perfusion is stopped, and the perfusate is thrice extracted with isopropyl acetate. Solvent is removed from the combined extracts by evaporation under reduced pressure, and the residue is crystallized by appropriate means.

Procedure B: microbiological oxidation. A stainless steel fermentation tank of 40-l. capacity is charged with a nutrient medium containing 3.3% dextrose, 0.5% cotton seed flour, 0.3% corn steep liquor, and 0.2% silicone antifoam in tap water. Tank and medium are sterilized by heating to a temperature of 120° and then cooled to about 25°, whereupon the medium is inoculated with an aqueous suspension of spores from a culture of *Rhizopus sp.* A.T.C.C. 13429. The culture is maintained at about 25° for 24 to 48 hr., during which time a stream of sterile air is passed through it at the rate of about 0.3 l. of air per l. of culture per minute. The culture is stirred continuously by means of a vertically-mounted mechanical agitator in order to produce submerged growth. Sufficient steroid dissolved in a minimal quantity of acetone is then introduced to bring the concentration of steroid to 1 part per 3000 parts of medium. Agitation and aeration are continued for 12 to 16 hr., at the end of which time the resultant mixture is extracted with dichloromethane. The extract is dried over anhydrous sodium sulfate and stripped of solvent by distillation. The residual oil, on trituration with anhydrous ether, crystallizes.

3-(3-Oxo-11β,17β-dihydroxy-19-nor-4-androsten-17α-yl)propanic acid lactone (IIb). According to procedure A, 1.0 g. of 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (Ib) was perfused through adrenal glands. The residual oil obtained was triturated with 50 ml. of benzene and the mixture filtered. The crude precipitate weighed 600 mg. and melted at 208–218°. A total of 401 mg. was recovered in two crops by recrystallization from 10 ml. of absolute ethanol. The analytical sample (1st crop) melted at 213–215° (solidified and remelted at 220–222°), and showed $[\alpha]_D$ +40° (diox.), $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 17,700).

(11) O. Hechter, R. P. Jacobsen, V. Schenker, H. Levy, R. W. Jeanloz, C. W. Marshall, and G. Pincus, *Endocrinology*, 52, 679 (1953).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.26; H, 8.17.

3-(3,11-Dioxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic lactone (IIa). A solution of IIb, 130 mg., in 5 ml. of acetone was treated with 0.17 ml. of a reagent containing 100 g. of chromic acid per 500 ml. of 6*N* sulfuric acid solution. The mixture was filtered and the filtrate evaporated to dryness. Recrystallization of the residue from methanol yielded 70 mg. of IIa, m.p. 234–237°, $[\alpha]_D$ +117° (diox.), $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,000).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.68; H, 7.83.

Similar oxidation of 100 mg. of IIc yielded 53 mg. of the identical ketone as demonstrated by mixed melting point and infrared spectra.

3-(3-Oxo-11α,17β-dihydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (IIc). Using Procedure B, 10 g. of 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (Ib) was hydroxylated. The crude crystalline product (500 mg.) was recrystallized several times from ethyl acetate to give a total of 377 mg. of product, m.p. 138–140° in several crops. An analytical sample showed m.p. 140–142°, $[\alpha]_D$ −66° (diox.), and $\lambda_{max}^{CH_3OH}$ 240.5 mμ (ε 17,000).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.87; H, 8.21.

3-(3-Oxo-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIe). One gram of 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (Ia) was oxidized according to Procedure A. The crude residue was chromatographed on 60 g. of silica gel. Elution with a solvent mixture of benzene–ethyl acetate (3:1) yielded 213 mg. of product. Upon recrystallization from ethyl acetate there was obtained in two crops, a total of 157 mg. of product, m.p. 205–208°, showing $[\alpha]_D$ +98° (diox.) and $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 16,250).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.66; H, 8.38.

3-(3,11-Dioxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IId). The hydroxyl compound IIe, 59 mg., was dissolved in 5 ml. of acetone and treated with 0.1 ml. of a reagent containing 100 g. of chromic acid per 500 ml. of 6*N* sulfuric acid solution. The mixture was filtered and the filtrate evaporated to dryness. Recrystallization of the residue from ethanol yielded 26 mg. of IId, m.p. 255–258°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 15,300).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.82; H, 8.03.

Similar oxidation of 100 mg. of IIf yielded 40 mg. of the identical ketone as demonstrated by mixed melting point and infrared spectra.

3-(3-Oxo-11α,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIf). According to procedure B, 10 g. of 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (Ia) was hydroxylated. The crude crystalline product was recrystallized successively from ethyl acetate and methanol to yield a total of 3.64 g. of product in several crops. The average melting point was 170–173°. The analytical sample melted at 173–174° and showed $[\alpha]_D$ +48.4° (diox.) and $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 15,900).

Anal. Calcd. for $C_{22}H_{30}O_4 \cdot {}^1/_2CH_3OH$: C, 72.29; H, 8.61. Found: C, 72.29; H, 8.52.

3-(3-Oxo-11α-mesyloxy-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IIg). To a solution of 1.07 g. of 3-(3-oxo-11α,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIf) in 4.2 ml. of chloroform and 1.0 ml. of pyridine was added at 0° with stirring over a 10 min. period 0.51 g. (1.5 mol. equiv.) of methanesulfonyl chloride dissolved in 1.0 ml. of chloroform. After 16 hr. of refrigeration the reaction mixture was diluted with 3 volumes of chloroform and washed successively with water, dilute aqueous sulfuric acid, water, dilute aqueous sodium bicarbonate, and finally water. After drying over sodium sulfate the chloroform solution was evaporated at temperatures less

than 25° to a sirupy residue and 30 ml. of absolute ethanol was added. Refrigeration for several hours produced a first crop of 670 mg. and concentration of the mother liquors produced an additional 130 mg., m.p. 157–163° (dec.).

Anal. Calcd. for $C_{23}H_{32}O_6S$: C, 63.27; H, 7.39. Found: C, 63.21; H, 7.15.

3-[3-Oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (III). To a solution of 1.85 g. of anhydrous sodium acetate in 16.6 ml. of glacial acetic acid heated in a Woods metal bath at a bath temperature of 112° was added over a 2 min. period 1.35 g. of 3-(3-oxo-11α-mesyloxy-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IIg). The bath temperature was maintained at 112° for an additional 30 min. and the reaction mixture was intermittently stirred during this period. The reaction mixture was then promptly cooled to room temperature and diluted with 33 ml. of water. Refrigeration produced 500 mg. of crystalline product, m.p. 155.5–157°. An analytically pure sample was obtained by recrystallization from ethyl acetate, m.p. 157.5–158°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,000).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.66; H, 8.14.

3-(3-Oxo-9α-bromo-11β,17α-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVa). A reaction mixture composed of 10.35 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (III), 5.20 g. of *N*-bromoacetamide and 165 ml. of peroxide-free dioxane was stirred at room temperature and 16.5 ml. of 1*N* perchloric acid was added all at once. After stirring for an additional 10 min. 560 ml. of 2% aqueous sodium bisulfite was added and then the reaction mixture was cooled to 5°. The precipitate was collected on a funnel, washed with water, and air dried to yield 7.7 g. of crude product. An analytically pure sample was obtained by recrystallization from ethanol, m.p. 162–164°, $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 16,300).

Anal. Calcd. for $C_{22}H_{29}BrO_4$: C, 60.41; H, 6.68. Found: C, 60.43, 60.41; H, 7.18, 6.94.

3-(3-Oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (V). A solution of 580 mg. of anhydrous potassium acetate in 5.85 ml. of absolute ethanol was heated to the boiling point and then the heat source was removed. A solution of 850 mg. of 3-(3-oxo-9α-bromo-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVa) in 2.75 ml. of peroxide-free dioxane was promptly added. The reaction mixture was brought rapidly to reflux, maintained there for 40 min., and then promptly cooled in an ice bath. Addition of 14.5 ml. of water and subsequent refrigeration for 2 hr. produced crystals which were recrystallized from acetone-hexane to yield 348 mg. of product. An analytically pure sample was obtained by recrystallization from methanol, m.p. 205–210°, $\lambda_{max}^{CH_3OH}$ 243 mμ (ε 14,500).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.70; H, 7.73.

3-(3-Oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVb). A solution of 29 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (V) in 2.75 ml. of redistilled chloroform was added dropwise to a cold (−50°) solution of 696 mg. of anhydrous hydrogen fluoride in 1.32 g. of redistilled tetrahydrofuran. The reaction mixture was held at 0° for 3.5 hr., diluted with four volumes of chloroform, and then washed successively with water, dilute aqueous sodium bicarbonate, and finally water. The chloroform solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to yield 6.5 mg., m.p. 276–278° (dec.), $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 16,100), $[\alpha]_D$ +168.4°.

Anal. Calcd. for $C_{22}H_{29}FO_4$: C, 70.19; H, 7.76. Found: 70.22; H, 7.68.

3-(3β,11β,17β-Trihydroxy-9α-fluoro-4-androsten-17α-yl)-propanoic acid lactone (VI). To a stirred suspension of 300 mg. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) in 35 ml. of methanol at 35° was added a solution of 250 mg. of sodium borohydride in 10 ml. of methanol. Stirring was continued for 35 min. when complete solution had been obtained and the reaction temperature was allowed to fall to room temperature. A solution of 4 ml. of glacial acetic acid in 15 ml. of water was slowly added and then the solution was evaporated *in vacuo* to one half of its original volume. Addition of 150 ml. of water was followed by concentrating again to one-half volume, producing a granular solid which was crystallized from aqueous ethanol to yield 200 mg. of VI, m.p. 143–146°, $[\alpha]_D$ +72.8°. Concentration of mother liquors produced an additional 50 mg. of product.

Anal. Calcd. for $C_{22}H_{31}FO_4$: C, 69.81; H, 8.26. Found: C, 69.51; H, 8.11.

3-(3,11-Dioxo-9α-fluoro-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVc). A solution of 200 mg. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) in 10 ml. of pyridine was added slowly with mixing to a pyridine–chromic acid complex prepared by adding 200 mg. of chromium trioxide slowly to 5 ml. of pyridine. During the addition of the steroid solution the reaction mixture was kept at 20° with external cooling and maintained at that temperature for 15 min. afterwards. After standing at room temperature overnight the reaction mixture was transferred slowly into a two-phase solvent mixture of 50 ml. of ethyl acetate and 25 ml. of water. The ethyl acetate layer was separated and combined with one ethyl acetate extract of the aqueous layer. The combined ethyl acetate extracts were washed successively with water, dilute hydrochloric acid, and water. After drying over sodium sulfate the solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from ethyl acetate–hexane to yield 71 mg., m.p. 238–239°, $[\alpha]_D$ +96°, infrared ($CHCl_3$), 5.62μ, 5.76μ, 5.97μ.

Anal. Calcd. for $C_{22}H_{27}FO_4$: C, 70.56; H, 7.27. Found: C, 70.36; H, 7.12.

Acknowledgment. The authors wish to thank Dr. R. R. Burtner for his interest and helpful suggestions throughout the course of this work.

CHICAGO 80, ILL.