afford 1.1 g. (90%) of the crude product, m.p. 190–194°. Recrystallization from aqueous methanol gave the analytical sample, m.p. 195–197°; $[\alpha]^{25}D$ −84° (*c* 1% in methanol); λ_{max}^{EtOH} 2.90, 4.50, and 5.96 μ.

Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93. Found: C, 77.09; H, 8.80.

Pregn-4-ene-3,20-dione-19-nitrile (XXV).—A solution of 0.6 g. (0.00185 mole) of XXIV in 100 ml. of acetone was treated with 1.8 ml. of 8 *N* chromic acid reagent as described for the preparation of XI. There was obtained 0.55 g. (90%) of the Δ^5 dione, m.p. 178–186°, which was chromatographed on alkaline alumina (25 g.) to give 0.40 g. (66% over-all yield) of XXV, m.p. 155–158°, from the 2% methanol in ether fractions. Recrystallization from acetone–hexane gave the analytical sample, m.p. 161–162°; $[\alpha]^{25}D$ +244° (*c* 1% in $CHCl_3$); λ_{max}^{EtOH} 4.50, 5.92, 5.97, and 6.15 μ; λ_{max}^{EtOH} 232 μ (ε 16,800).

Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36. Found: C, 77.63; H, 8.41.

Steroidal Aldosterone Blockers. VII[1]

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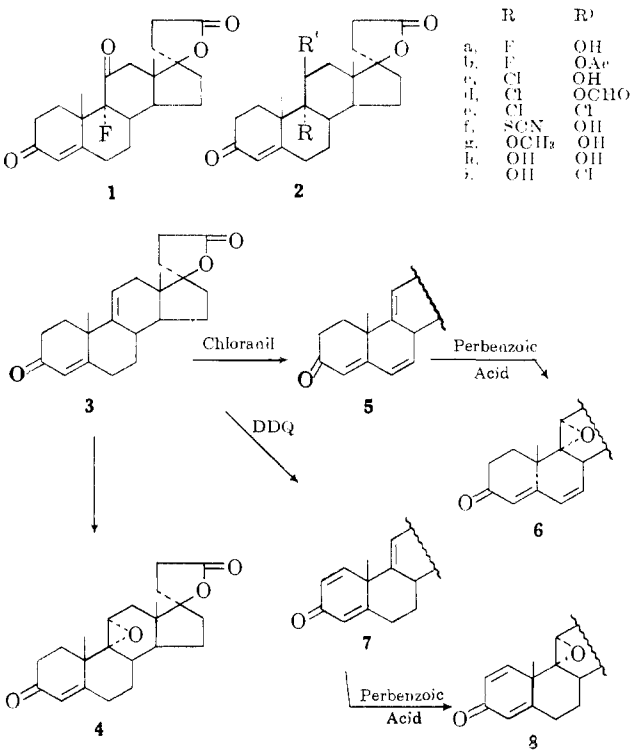
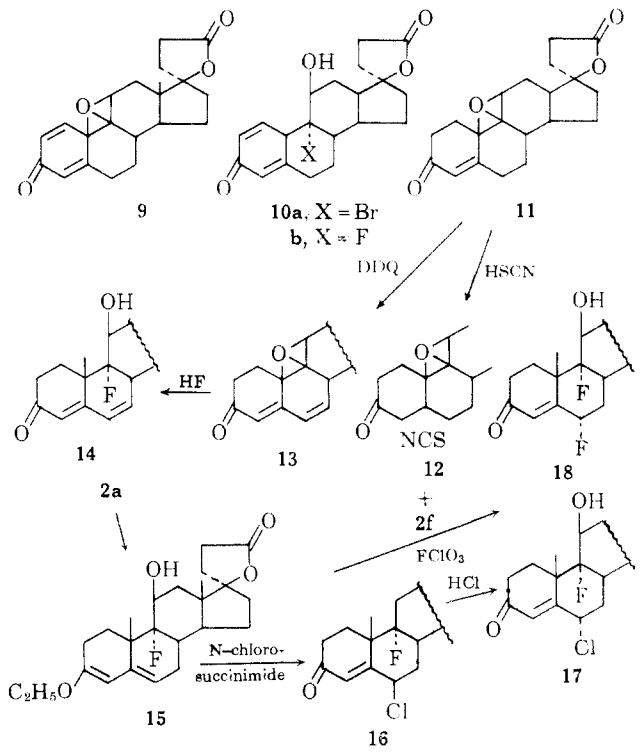
A number of steroidal 17-spirolactones bearing substituents at positions 9 and 11 have been prepared. The syntheses and biological activities are described.

Previous papers[1a] in this series have reported the synthesis of a variety of steroids which were prepared in the search for aldosterone blocking activity. One of the most interesting steroids was 3-(3,11-dioxo-9α-fluoro-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**1**).[1b] We were led therefore to prepare other steroidal 17-spirolactones bearing substituents at C-9 and C-11.



All of the steroids reported herein were prepared from spirolactones previously reported[1b] using, for the most part, standard methods to obtain the expected products. Treatment of 3-[3-oxo-9α,11α-oxido-17β-hydroxy-4-androsten-17α-yl] propanoic acid lactone (**4**) in methylene chloride solution with hydrochloric acid gave the expected *trans*-diaxial 9α-hydroxy-11β-chloro derivative (**2f**).

When a chloroform solution of thiocyanic acid was added to the 9β,11β-epoxide (**11**)[2], fractional crystallization techniques produced two addition products. On the basis of spectral evidence one was assigned as the 9α-thiocyano-11β-hydroxy derivative (**2f**), and the other was tentatively assigned as the 5ξ-isothiocyano-9β,11β-epoxide (**12**).



Additional unsaturation was produced in the 3-oxo-4-ene-9β,11β-epoxy system with 2,3-dichloro-5,6-dicyanobenzoquinone in dioxane solution at reflux to give the 3-oxo-4,6-diene (**13**), characterized by the absorption maximum at 280 mμ in the ultraviolet. This was somewhat unexpected since treatment with this react-

(1) (a) Paper VI: L. N. Nysted and R. R. Burtner, *J. Org. Chem.*, **27**, 3175 (1962); (b) E. A. Brown, R. D. Moir, and J. A. Cella, *ibid.*, **25**, 96 (1960).

(2) K. Takeda and T. Kondoo, *Chem. Pharm. Bull.* (Tokyo), **8**, 408 (1960).

ant generally produces unsaturation at C-1 in the steroid nucleus.

The biological studies reported in Table I were conducted by Dr. C. M. Kagawa and Mr. Robert Jacobs of these laboratories. It has been demonstrated that a definite and proportional relationship exists between the blocking effects of typical steroidal spirolactones when tested on rats treated with aldosterone and deoxycorticosterone acetate (DOCA).[3] The more available deoxycorticosterone acetate was employed as the sodium retaining agent throughout this work. Those compounds which were inactive at doses of 2.4 mg./rat have been omitted from the table.

TABLE I

DEOXYCORTICOSTERONE ACETATE BLOCKING POTENCIES

Compound	MED[a]	Compound	MED
1	0.04	**4**	0.11
2a	0.22	**7**	0.28
2b	>0.6	**8**	1.6
2c	>0.6	**10a**	>0.5
2d	>0.3	**10b**	1.8
2f	>0.6	**11**	>1.2
2g	1.7	**12**	>0.6
2h	>0.6	**14**	>1.0
2i	0.20	**15**	>0.6
3	0.53	**16**	>0.6
		18	>0.9

[a] MED is the minimal effective dose (mg./rat) which, when used with 12 γ of DOCA in adrenalectomized rats, produces the same urinary sodium/potassium ratio as that which results from the use of 6 γ of DOCA alone. All of the results in Table I are for s.c. administration.

Experimental

The microanalyses and optical determinations were carried out by Dr. Robert T. Dillon and his associates of these Laboratories. Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument in deuteriochloroform solution with tetramethylsilane as internal standard and peaks are reported in cycles per second downfield. Ultraviolet spectra were determined in methanol. Melting points were determined on a Fisher–Johns block.

3-(3-Oxo-9α,11α-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic Acid Lactone (4).—To a solution of 1.35 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl] propanoic acid lactone (**3**)[1b] in 25 ml. of anhydrous benzene was added 10 ml. of a solution of 0.61 *M* perbenzoic acid in benzene. This reaction solution was held at 5° for 24 hr. and then at room temperature for 48 hr. Addition of 35 ml. of hexane produced separation of 1.0 g. of a crystalline solid. Analytically pure product was obtained by recrystallization from acetone, m.p. 252–256° dec.; λ_{max} 238 mμ (ϵ 15,700); infrared ($CHCl_3$), 5.62 and 5.94 μ.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.43; H, 8.08.

3-(3-Oxo-9α,17β-dihydroxy-11β-chloro-4-androsten-17α-yl)propanoic Acid Lactone (2i).—A reaction mixture of 1.0 g. of 3-(3-oxo-9α,11α-oxido-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (**4**), 60 ml. of methylene chloride, and 60 ml. of concentrated hydrochloric acid was stirred vigorously at room temperature for 15 min. The lower layer was separated and washed successively with water, dilute aqueous potassium bicarbonate, and water, and finally it was dried over sodium sulfate. The solvent was evaporated under nitrogen; the tacky residue crystallized when 2 ml. of ethyl acetate was added, yielding 650 mg. of the chlorohydrin (**2i**), m.p. 186–189° dec.; λ_{max} 240 mμ (ϵ 15,250); n.m.r. 78, 101, 260(C-11-αH), 350 c.p.s. (C_4H); infrared (KBr), 2.87, 5.60, and 6.01 μ.

Anal. Calcd. for $C_{22}H_{29}ClO_4$: C, 67.25; H, 7.44. Found: C, 67.10; H, 7.44.

3-[3-Oxo-17β-hydroxy-4,6,9(11)-androstatrien-17α-yl]propanoic Acid Lactone (5).—A reaction mixture of 2.0 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (**3**),[1b] 4.0 g. of chloranil, and 140 ml. of *t*-butyl alcohol was stirred and refluxed for 5 hr.[4] The precipitate was removed by filtration and the filtrate was evaporated *in vacuo* to dryness. The residue was taken up in chloroform and washed successively with water, 5% aqueous sodium bicarbonate, and finally water. After drying the solution over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was dissolved in 500 ml. of benzene and chromatographed through a column of 150 g. of silica gel. The desired triene (654 mg.) was obtained as an oil from the peak fractions eluted with ethyl acetate–benzene (1:9); λ_{max} 282 mμ (ϵ 20,500); infrared ($CHCl_3$), 5.64, 6.01, 6.16, and 6.32 μ.

3-(3-Oxo-9α,11α-oxido-17β-hydroxy-4,6-androstadien-17-yl)propanoic Acid Lactone (6).—To 529 mg. of 3-[3-oxo-17α-hydroxy-4,6,9(11)-androstatrien-17α-yl]propanoic acid lactone (**5**) was added 15 ml. of a solution of 0.16 *M* perbenzoic acid in benzene. The resulting solution was maintained at 5° for 72 hr. and then at room temperature for 24 hr. Addition of 15 ml. of hexane produced a tan precipitate (500 mg.) which was recrystallized first from ethyl acetate and then from acetone, m.p. 292–295° dec.; λ_{max} 281 mμ (ϵ 22,600); infrared (KBr), 5.65, 6.02, 6.20, and 6.32 μ.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.27; H, 7.41.

3-[3-Oxo-17β-hydroxy-1,4,9(11)-androstatrien-17α-yl]propanoic Acid Lactone (7).—A reaction mixture of 1.02 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (**3**), 794 mg. of 2,3-dichloro-5,6-dicyanobenzoquinone, and 25 ml. of anhydrous benzene was stirred and refluxed for 20 hr. The precipitate was removed by filtration and the filtrate was diluted with 50 ml. of benzene and 25 ml. of ethyl ether before it was washed in a separatory funnel twice with 2% aqueous sodium sulfite and then three times with water. After drying the solution over sodium sulfate the solvent was evaporated *in vacuo* and the residue crystallized from 4 ml. of methanol to yield 650 mg. of **7**, m.p. 86–90° (solvated with methanol), λ_{max} 240 mμ (ϵ 14,800); infrared ($CHCl_3$), 2.72, 2.93, 5.61, 5.97, 6.12, and 6.20 μ; n.m.r. 338 (center of multiplet for C-11 H); 363–385 (multiplet for C-2 H and C-4 H); 440 c.p.s. (C-1 H). For elemental analysis a sample was dried at 78° *in vacuo* for 5 hr.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 77.98; H, 7.78.

3-(3-Oxo-9α,11α-oxido-17β-hydroxy-1,4-androstadien-17α-yl)propanoic Acid Lactone (8).—To 1.35 g. of 3-[3-oxo-17β-hydroxy-1,4,9(11)-androstatrien-17α-yl]propanoic acid lactone (**7**) was added 36 ml. of a solution of 0.16 *M* perbenzoic acid in benzene. The resulting solution was held at 5° for 96 hr. and then at room temperature for 24 hr. Addition of 50 ml. of hexane produced separation of an oil which became partly crystalline. Recrystallization from ethyl acetate produced 620 mg. of crude product in two crops. Further recrystallization from acetone–hexane provided an analytical sample, m.p. 244–249° dec.; λ_{max} 237.5 mμ (ϵ 13,500); infrared ($CHCl_3$), 5.63, 5.98, 6.12, and 6.20 μ.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.30; H, 7.40.

3-(3-Oxo-9α-bromo-11β,17β-dihydroxy-1,4-androstadien-17α-yl)propanoic Acid Lactone (10a).—A reaction mixture of 2.41 g. of 3-(3-oxo-17β-hydroxy-1,4,9(11)-androstatrien-17α-yl)-propanoic acid lactone (**7**), 11.1 ml. of *N* perchloric acid, and 111 ml. of peroxide-free dioxane was stirred at room temperature and 2.5 g. of *N*-bromoacetamide was added all at once.[5] After stirring for an additional 20 min., 90 ml. of 2% aqueous sodium sulfite was added followed by 500 ml. of water; the resulting precipitate was collected, washed with water, and air-dried to yield 2.5 g. of crude product. Recrystallization from ethanol yielded an analytical sample, m.p. 173–176° dec.; infrared ($CHCl_3$), 2.72, 2.86, 5.63, 5.98, 6.13, and 6.20 μ.

Anal. Calcd. for $C_{22}H_{27}BrO_4$: C, 60.69; H, 6.25. Found: C, 60.92; H, 6.38.

3-(3-Oxo-9β,11β-oxido-17β-hydroxy-1,4-androstadien-17α-yl)propanoic Acid Lactone (9).—To a solution of 1.9 g. of 3-(3-oxo-9α-bromo-11β,17β-dihydroxy-1,4-androstadien-17α-yl)propanoic acid lactone (**10a**) in 72 ml. of tetrahydrofuran

(3) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(4) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957).

(5) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

was added a solution of 475 mg. of sodium carbonate in 33 ml. of water. The resulting solution was stirred at room temperature for 20 hr. and then 1.6 ml. of glacial acetic acid was added. After evaporation of one-half of the solvent *in vacuo*, 60 ml. of water was added, producing an oil which quickly congealed. The solid product was collected on a funnel, washed with water, and crystallized from acetone–hexane to yield 900 mg. of solvated (acetone) product which liquefied at 122–130° and then resolidified and melted at 168°. An analytical sample was dried for 3 hr. at 78° *in vacuo*; infrared ($CHCl_3$), 5.62, 5.80, 5.98, 6.12, and 6.20 μ.

Anal. Calcd. for $C_{22}H_{26}O_4 \cdot 0.5CH_3COCH_3$: C, 73.60; H, 7.62. Found: C, 73.94; H, 7.75.

3-(3-Oxo-9α-fluoro-11β,17β-dihydroxy-1,4-androstadien-17α-yl)propanoic Acid Lactone (10b). (a).—To 4 ml. of a cold (0°) 31% solution of hydrogen fluoride in tetrahydrofuran was added 200 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-1,4-androstadien-17α-yl)propanoic acid lactone (**9**). The resulting solution was held at −5° for 24 hr. and then transferred into 20 ml. of cold water. The precipitate was collected, washed with water, dried, and then crystallized from ethyl acetate to yield 100 mg. of product as the monohydrate; m.p. 139°, resolidified and melted at 228–232° dec.; λ_{max} 238 mμ (ε 14,900); infrared ($CHCl_3$), 2.69, 2.75, 2.88, 5.64, 5.98, 6.14, and 6.21 μ.

Anal. Calcd. for $C_{22}H_{27}FO_4 \cdot H_2O$: C, 67.33; H, 7.45. Found: C, 67.27; H, 7.47.

(b).—A reaction mixture of 1.0 g. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (**2a**),[6] 670 mg. of 2,3-dichloro-5,6-dicyanobenzoquinone, and 75 ml. of peroxide-free dioxane was stirred and refluxed for 20 hr. After cooling to room temperature, the reaction mixture was filtered and the filtrate was diluted with 200 ml. of water producing 700 mg. of crude product as a yellow solid. Recrystallization from ethyl acetate and then twice from acetone gave a monohydrated product with an infrared spectrum identical with that prepared by the first method.

Anal. Found: C, 67.02; H, 7.82.

3-(3-Oxo-9α,11β-dichloro-17β-hydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2e).—A solution of 1.0 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (**3**) and 4.0 g. of lithium chloride in 40 ml. of glacial acetic acid was cooled in an ice bath and 430 mg. of N-chlorosuccinimide was added.[6] Immediately, 1.22 ml. of tetrahydrofuran containing 120 mg. of anhydrous hydrogen chloride was added. The resulting solution was stirred at room temperature for 3 hr. and then transferred into 400 ml. of water. The precipitate was collected, washed with water, and dried; it was crystallized from ethyl acetate to yield 310 mg. of the dichloride (**2e**), m.p. 192–196° dec.; λ_{max} 238 mμ (ε 15,400); infrared ($CHCl_3$) 5.63, 5.97, and 6.15 μ.

Anal. Calcd. for $C_{22}H_{28}Cl_2O_4$: C, 64.23; H, 6.86. Found: C, 63.92; H, 6.93.

3-(3-Oxo-9α-chloro-11β-formoxy-4-androsten-17α-yl)propanoic Acid Lactone (2d).—To a solution of 40 g. of sodium formate in 400 ml. of formic acid was added 10 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (**3**) and then 4.4 g. of N-chlorosuccinimide followed at once by 27 ml. of *N* hydrochloric acid.[7] This solution was stirred for 3 hr. at room temperature and then transferred into 4.0 l. of water. The precipitate was collected, washed with water, dried, and crystallized from acetone to yield 2.45 g. of product which was further purified by recrystallization from acetone, m.p. 218–220° dec.; infrared ($CHCl_3$), 5.62, 5.75, 5.96, and 6.13 μ.

Anal. Calcd. for $C_{23}H_{29}ClO_5$: C, 65.63; H, 6.94. Found: C, 65.43; H, 6.98.

3-(3-Oxo-9α,11β,17β-trihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2h).—To a solution of 7.13 g. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**11**);[6b] in 300 ml. of tetrahydrofuran was added 100 ml. of 3 *N* perchloric acid.[8] The resulting solution was held at room temperature for 18 hr. and then transferred into 1.8 l. of a saturated aqueous solution of sodium bicarbonate. The precipitate was collected on a funnel, washed with water, and dried to yield 4.4 g. of crude product which was crystallized from 300 ml. of methanol to yield 1.75 g. of the diol (**2h**), m.p. 277–278° dec.; infrared (KBr), 2.81, 2.87, 5.64, 6.01, and 6.12 μ.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.43; H, 8.05.

3-(3-Oxo-9α-methoxy-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2g).—To a solution of 1.0 g. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**11**) in 50 ml. of methanol was added 0.38 ml. of 72% perchloric acid.[8] The resulting solution was held at room temperature for 4 hr. and then neutralized (to alk-acid test paper) with a 2% aqueous solution of potassium bicarbonate. Water was added to a total solution volume of 100 ml. and the mixture was stored at 5° for 18 hr. producing a granular precipitate (400 mg.). The aqueous filtrate was evaporated *in vacuo* to remove the methanol and this produced an additional 400 mg. of crude product. These two crops were combined and recrystallized three times from methanol to yield 230 mg., m.p. 242–243°; λ_{max} 243 mμ (ε 15,350); infrared ($CHCl_3$), 2.75, 2.87, 5.65, and 6.01 μ.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.15; H, 8.22.

3-(3-Oxo-9α-chloro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2c).—To a stirred solution of 356 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**11**) in 3.6 ml. of redistilled chloroform was added at 0° over 3 min. 5 ml. of a cold (0°) 0.003 *M* solution of hydrogen chloride in redistilled chloroform.[5] The resulting solution was maintained at 0° for 1 hr. and then washed in a separatory funnel three times with water. It was then dried over sodium sulfate and evaporated under nitrogen to dryness. The crystalline residue was recrystallized from acetone to yield 80 mg. of **2c**, m.p. 225–227° dec.; infrared (KBr), 2.88, 5.65, 5.95, and 6.14 μ.

Anal. Calcd. for $C_{22}H_{29}ClO_4$: C, 67.25; H, 7.44. Found: C, 67.32; H, 7.39.

3-(3-Oxo-9α-thiocyano-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2f) and 3-(3-Oxo-5ξ-isothiocyano-9β,-11β-oxido-androstan-17α-yl)propanoic Acid Lactone (12).—A solution of thiocyanic acid in chloroform was prepared by shaking in a separatory funnel 20 g. of potassium thiocyanate, 34 g. of powdered potassium bisulfate, and 70 ml. of chloroform. The slurry was filtered and the filtrate made up to a volume of 70 ml. with additional chloroform. To 8.8 ml. of this chloroform solution 750 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**11**) was added and the resulting solution was held at room temperature for 24 hr.[2] After washing in a separatory funnel successively with water, dilute sodium bicarbonate solution, and then water, the chloroform solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. Digestion of the residue with 40 ml. of boiling ethyl acetate left 50 mg. of a substance which remained undissolved in the hot solvent. This insoluble substance was recrystallized from methanol to yield 34 mg. of the 9α-thiocyano derivative (**2f**), m.p. 160–161.5° dec.; infrared ($CHCl_3$), 2.88, 4.66, 5.63, 5.96, and 6.15 μ.

Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03. Found: C, 66.55; H, 6.95.

The hot ethyl acetate solution (from digestion of the crude residue) on cooling to 5° produced 200 mg. of the 5ξ-isothiocyano derivative (**12**), m.p. 173–175° dec.; infrared ($CHCl_3$), 4.75, 5.63, 5.78 μ; n.m.r. 68 (C-18-CH_3), 82 (C-19-CH_3), 212 c.p.s. (C-11-αH).

Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03. Found: C, 66.41; H, 7.08.

3-(3-Oxo-9β,11β-oxido-17β-hydroxy-4,6-androstadien-17α-yl)propanoic Acid Lactone (13).—A reaction mixture of 1.0 g. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (**11**), 0.7 g. of 2,3-dichloro-5,6-dicyanobenzoquinone, and 75 ml. of peroxide-free dioxane was stirred and refluxed for 20 hr. After cooling to room temperature, the precipitate was removed by filtration and the filtrate was evaporated *in vacuo* to a volume of 10 ml. which was then diluted with 90 ml. of water. The resulting aqueous slurry was extracted with benzene and the benzene layer was washed twice with a total of 100 ml. of 2% sodium sulfite solution and then finally washed with water. After drying over sodium sulfate the solvent was removed *in vacuo* to afford a solid residue which was crystallized from ethyl acetate to yield 500 mg. of crude diene (**13**). Recrystallization from methanol, ethyl acetate, and then again from methanol

(6) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959).

(7) C. H. Robinson, L. Finckenor, M. Kiefley, D. Gould, and E. P. Oliveto, *ibid.*, **81**, 2195 (1959).

(8) P. Littell and S. Bernstein, *ibid.*, **78**, 981 (1956).

yielded an analytical sample, m.p. 212–216°, λ_{max} 280 mμ (ε 20,200); infrared ($CHCl_3$) 5.62, 5.99, 6.10, and 6.28 μ.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.67; H, 7.37.

3-(3-Oxo-9α-fluoro-11β,17β-dihydroxy-4,6-androstadien-17α-yl)propanoic Acid Lactone (14). (a).—A reaction mixture of 1.0 g. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (**2a**), 1.75 g. of chloranil, and 71 ml. of *t*-butyl alcohol was stirred and refluxed for 4 hr. and then cooled to room temperature and filtered.[4] The filtrate was evaporated *in vacuo* and the residue was taken up in 75 ml. of chloroform. The chloroform solution was washed in a separatory funnel twice with water, four times with 5% sodium bicarbonate solution, and finally twice with water. After it was dried over sodium sulfate, the solution was evaporated to dryness *in vacuo*. The residue was triturated with 25 ml. of diethyl ether and the insoluble portion was crystallized from ethyl acetate to yield 150 mg. of crude diene (**14**). An analytical sample, as the hemihydrate, was obtained by recrystallization from ethyl acetate, m.p. 296–300° dec., change of state 159°; λ_{max} 280 mμ (ε 24,400); infrared (KBr), 2.92, 5.67, 6.02, 6.16, and 6.30 μ.

Anal. Calcd. for $C_{22}H_{27}FO_4 \cdot 0.5H_2O$: C, 68.91; H, 7.31. Found: C, 68.90; H, 7.31.

(**b**).—To 4 ml. of a 31% solution of hydrogen fluoride in tetrahydrofuran maintained at −25° was added 40 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4,6-androstadien-17α-yl)-propanoic acid lactone (**13**). After 5 hr. at −25° the solution was diluted with 20 ml. of water and the resulting precipitate was collected on a funnel, washed with water, and dried to yield 40 mg. of product, m.p. 294° dec.; infrared (KBr) identical with that for the product prepared by the preceding method (a).

3-(3-Oxo-9α-fluoro-11β-acetoxy-17β-hydroxy-4-androsten-17α-yl)propanoic Acid Lactone (2b).—A reaction mixture of 600 mg. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (**2a**), 2.5 ml. of acetic anhydride, and 10 ml. of pyridine was heated at 80° for 16 hr., cooled to room temperature, and 5 ml. of methanol was added. After removal of solvent *in vacuo* the residue was dissolved in 100 ml. of benzene and chromatographed through a column of 30 g. of silica gel. Elution with ethyl acetate–benzene (2:8) produced 420 mg. of product (**2b**) which was purified by recrystallization from ethyl acetate to yield an analytical sample, m.p. 209–213°; infrared (KBr), 5.61, 5.68, 5.96, and 6.15 μ.

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 68.88; H, 7.47. Found: C, 68.90; H, 7.48.

3-(3-Ethoxy-9α-fluoro-11β,17β-dihydroxy-3,5-androstadien-17α-yl)propanoic Acid Lactone (15).—A reaction mixture of 2.0 g. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (**2a**), 2.0 ml. of triethyl orthoformate, 100 mg. of *p*-toluenesulfonic acid monohydrate, and 15.2 ml. of peroxide-free dioxane was stirred at room temperature for 90 min. during which time complete solution of the steroid occurred. After adding 1.6 ml. of pyridine, the solution was transferred into 120 ml. of ice and water. The precipitate was collected on a funnel, washed with water, dried, and recrystallized from 110 ml. of methanol containing two drops of added pyridine to yield 1.4 g. of product, λ_{max} 240 mμ (ε 28,800), infrared (KBr), 2.79, 5.62, 6.01, and 6.11 μ. For elemental analysis a sample was recrystallized a second time from methanol, m.p. 209–215° dec.

Anal. Calcd. for $C_{24}H_{33}FO_4$: C, 71.26; H, 8.22. Found: C, 71.08; H, 8.36.

3-(3-Oxo-6β-chloro-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (16).—To a stirred solution of 808 mg. of 3-(3-ethoxy-9α-fluoro-11β,17β-dihydroxy-3,5-androstadien-17α-yl)propanoic acid lactone (**15**) in 24 ml. of acetone was added a solution of 508 mg. of sodium acetate in 3.2 ml. of water. The resulting suspension was cooled in ice, stirred, and maintained at 5° while 540 mg. of N-chlorosuccinimide and 0.62 ml. of glacial acetic acid were added. Stirring at 5° was continued for 2.5 hr. and then the reaction mixture was allowed to stand at 5° for 18 hr. Upon gradual addition of 125 ml. of water the suspension first becomes a clear solution, and then a precipitate was formed which was collected, washed with water, and dried. After removal of a small amount (25 mg.) of a highly insoluble impurity by addition of hexane to an acetone solution of the crude product, 530 mg. of product was obtained by further dilution of the filtrate with hexane. Recrystallization from ethyl acetate–hexane yielded an analytical sample, m.p. 185–189° dec.; λ_{max} 237 mμ (ε 13,300); infrared ($CHCl_3$), 2.73, 2.87, 5.64, 5.94 μ; n.m.r. 78 (C-18–CH_3), 111 (C-19–CH_3), 255–270 (C-6–αH), 285–293 (C-11–αH), 358 c.p.s. (C-4–H).

Anal. Calcd. for $C_{22}H_{28}ClFO_4$: C, 64.30; H, 6.87. Found: C, 64.22; H, 7.28.

3-(3-Oxo-6α-chloro-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (17).—A solution of 200 mg. of 3-(3-oxo-6β-chloro-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (**16**) in 10 ml. of glacial acetic acid was maintained at 20° while anhydrous hydrogen chloride was bubbled through it. The solvent was then removed *in vacuo* and the tacky residue was crystallized from methanol and then recrystallized from 8 ml. of methanol to yield 90 mg. of the 6α-chloro steroid as the monomethanolate, m.p. 137–139° dec.; λ_{max} 233 mμ (ε 14,600); infrared ($CHCl_3$), 2.72, 2.85, 5.63, 5.93, and 6.13 μ.

Anal. Calcd. for $C_{22}H_{28}ClFO_4 \cdot CH_3OH$: C, 62.36; H, 7.28. Found: C, 62.21; H, 7.18.

3-(3-Oxo-6α,9α-difluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic Acid Lactone (18).—A solution of 600 mg. of 3-(3-ethoxy-9α-fluoro-11β,17β-dihydroxy-3,5-androstadien-17α-yl)propanoic acid lactone (**15**) in 5 ml. of pyridine was maintained at −20° while perchloryl fluoride was passed through it for 5 min.[9] The solution was then evacuated on a water aspirator to remove excess perchloryl fluoride, and 25 ml. of water was added. The precipitate which formed was collected, dissolved in 5 ml. of methanol, and then one drop of 20% hydrochloric acid was added. After holding the solution at room temperature for 2 hr., crude product was precipitated by dilution with water. Crystallization of the crude product from methanol, followed by trituration with several ml. of diethyl ether, yielded 100 mg. of 6α-fluoro steroid as the hemimethanolate; it liquefied at 136°, resolidified, and decomposed at 194–201°; λ_{max} 230 mμ (ε 11,700); infrared ($CHCl_3$); 2.72, 2.85, 5.62, 5.90, and 6.13 μ.

Anal. Calcd. for $C_{22}H_{28}F_2O_4 \cdot 0.5CH_3OH$: C, 65.83; H, 7.37. Found: C, 65.88; H, 7.27.

(9) S. Nakanishi, K. Morita, and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959).