C-19-Functional Steroids. VI.[1,2] Testosterone Derivatives[3]

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Syntheses of 17β-hydroxy-3-oxoandrost-4-ene-19-nitrile, some 17α-methyl-19-substituted testosterone derivatives, and 3,20-dioxopregn-4-ene-19-nitrile using 5α-chloro-6β-hydroxysteroid intermediates are described. Treatment of androstenediol diacetate with hypochlorous acid gave the corresponding chlorohydrin derivative. The nitrite ester derived from the foregoing chlorohydrin gave, on photolysis, 5α-chloro-19-oximino androstane-3β,6β,17β-triol 3,17-diacetate. By the action of zinc in hot acetic acid on the last compound there was obtained the corresponding Δ⁵ derivative, which, through a series of reactions, gave the testosterone analog. The progesterone derivative was obtained in a similar manner. The 17α-methyl compounds were obtained *via* treatment of 3β-hydroxy-17-oxoandrost-5-ene-19-nitrile with methylmagnesium bromide. A preliminary pharmacological examination of some of these compounds is discussed.

The 19-nor progestational and anabolic steroids demonstrate the pharmacological benefits of removal of the C-19 angular methyl group, but little is known of the effects of modification of this moiety. The purpose of the present work was to prepare compounds for examination of the pharmacological consequences of the replacement of the 19-methyl group by a nitrile function in progesterone and testosterone.

The C-19 modified steroids described in this study were prepared *via* the photolysis of 6β-nitrites. Previous methods used for the elaboration of the requisite 6β-hydroxy steroids from Δ⁵-steroids include the nitration of androst-5-ene-3β,17β-diol diacetate followed by conversion to the 6-ketone and reduction to the 6β-alcohol.[4] A newer method involves oxidation of a 5α-bromo-6β-hydroxy steroid to the 6-ketone, reductive removal of the bromine with zinc in acetic acid, and catalytic reduction of the ketone to the 6β-alcohol.[5] Regeneration of the Δ⁵ linkage of 19-oximino-6β-hydroxy-steroids by dehydration methods has been described[6] but concomitant dehydration of the oxime occurs and only the nitrile is obtained. In order to avoid these multistep sequences as well as the comparatively drastic dehydration step, a simpler scheme was sought.

The addition of hypochlorous acid to cholesteryl acetate to afford the corresponding 6β-hydroxy-5α-chloro derivative, and the reductive removal of the elements of hypochlorous acid to regenerate the double bond, have been described.[7] In the present work, nitrite esters derived from 6β-hydroxy-5α-chlorosteroids were utilized in the nitrite photolysis reaction[8] and the Δ⁵ linkage was directly regenerated with zinc acetic acid to afford the 19-oximino-Δ⁵-steroid. This reaction pattern is of general utility for the production of C-19 substituted steroids from the readily available Δ⁵-steroids, since the requisite 6β-hydroxy group can be introduced and removed in only two steps.

After some orienting experiments in the cholestane series, which are described in the Experimental section, treatment of androst-5-ene-3β,17β-diol diacetate with calcium hypochlorite and acetic acid gave the chlorohydrin I in 40% yield. By treatment of I with nitrosyl chloride in pyridine solution, the corresponding nitrite ester was obtained in crystalline form, but this substance was rather unstable and could not be recrystallized. Photolysis of the nitrite in toluene solution, using the diphenylamine–sulfuric acid test[9] to follow the reaction, gave the 19-nitroso derivative, which, on heating in 2-propanol, formed the oxime III in 41% over-all yield.

The structures III and IV were examined to determine whether the oxime function in these compounds is present as the *syn*, *anti*, or cyclized hydroxy amino form. Although the same question had been answered in this laboratory in the case of steroidal 2β-hydroxy-19-oximes by an n.m.r. method,[10] this technique could not be applied in the present case because the n.m.r. signals arising from the hydroxyl groups in III and IV were too broad to be useful. The infrared spectra of III and IV in dilute bromoform solution showed a free oxime hydroxyl group (sharp band at 2.81 μ) and an intramolecularly hydrogen-bonded hydroxyl function (broad band at 3.1–3.3 μ, unaffected by further dilution of the solution). These compounds are therefore *syn*-oximes in quasicyclic, intramolecularly hydrogen-bonded form, similar to the ones in the previous case. Acetylation of the oxime III gave V, which on melting formed a nitrile. This pyrolytic *cis* elimination of the elements of acetic acid is compatible with a *syn* configuration.[11]

Regeneration of the Δ⁵ linkage was smoothly effected by removal of the elements of hypochlorous acid from

(1) From the Ph.D. thesis of T. Jen, University of California, 1963. This investigation was supported by a PHS research grant 1AM-05016) from the National Institute of Arthritis and Metabolic Diseases, United States Public Health Service. The n.m.r. spectrometer used in this study was provided by a grant (NSF-G 21298) from the National Science Foundation.

(2) Paper V: T. Jen and M. E. Wolff, *J. Org. Chem.*, **28**, 1573 (1963).

(3) Preliminary accounts of portions of this work have been presented in (a) R. Kwok, T. Jen, and M. E. Wolff, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 43N; (b) T. Jen, R. Kwok, W. Ho, and M. E. Wolff, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 6-O; and (c) T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 879 (1962).

(4) D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.*, 245 (1953).

(5) A. Bowers, E. Denot, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(6) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **83**, 4076 (1961).

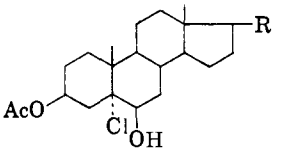
(7) S. Mori, *J. Chem. Soc. Japan*, **64**, 981 (1943).

(8) Independently of our initial disclosure of this sequence in ref. 3, the use of 6β-hydroxy-5α-halosteroids for C-19 functionalization was reported by (a) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **84**, 1496 (1962), (nitrite photolysis); (b) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *ibid.*, **84**, 3204 (1962), (lead tetraacetate oxidation); and (c) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962) (lead tetraacetate oxidation).

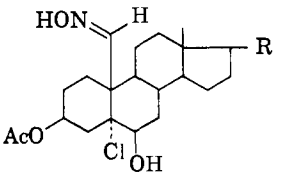
(9) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1960, p. 178.

(10) R. Kwok and M. E. Wolff, *Chem. Ind. (London)*, 1251 (1962); *J. Org. Chem.*, **28**, 423 (1963).

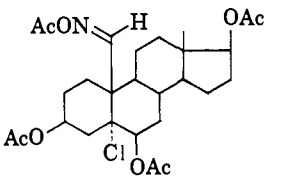
(11) D. Ambrose and G. L. Brady, *J. Chem. Soc.*, 1243 (1952).



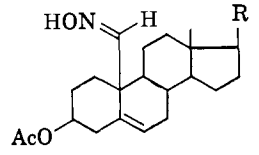
I R = OAc
II R = C_8H_{17}
XX R = CH_3CO



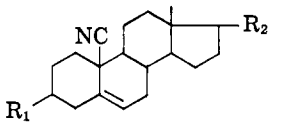
III R = OAc
IV R = C_8H_{17}
XXI R = CH_3CO



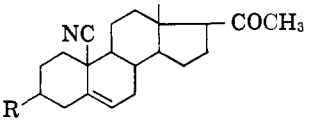
V



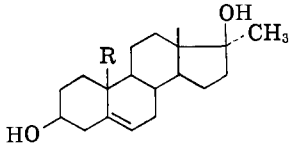
VI R = OAc
VII R = C_8H_{17}
XXII R = CH_3CO



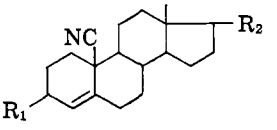
VIII R_1 = OAc, R_2 = OAc
IX R_1 = OH, R_2 = OH
X R_1 = OH, R_2 = O
XI R_1 = O, R_2 = O



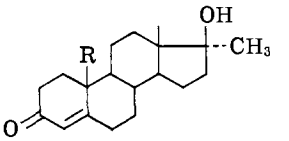
XXIII R = OAc
XXIV R = OH



XII R = CN XIV R = CH_2OH
XIII R = CHO



XV R_1 = O, R_2 = O
XVI R_1 = OH, R_2 = OH
XVII R_1 = O, R_2 = OH
XXV R_1 = O R_2 = CH_3CO



XVIII R = CN
XIX R = CH_2OH

III with zinc in acetic acid at 90–95° for 30 min. to afford VI. Higher temperatures resulted in partial acetylation and subsequent dehydration of the 19-oxime to give a mixture of products. This *trans* elimination of hypochlorous acid, taken together with the previously discussed infrared data, constitutes convincing evidence that no epimerization of the 6β-hydroxy group takes place during the photolysis, in contrast to the reported[12] photolytic epimerization of another nitrite.

The oxime VI was readily dehydrated with acetic anhydride to afford the nitrile VIII on a preparative scale. Hydrolysis of VIII gave the diol IX[13] and oxidation to the 3-oxo-Δ^4 system was then undertaken. Although Oppenauer oxidation is often used for this conversion, in the present case it was found that oxidation of IX gave a resinous mixture which was difficult to separate by chromatography. Oxidation with chromic acid in acetone[14] was more successful. Thus, selective (5 min.) oxidation of IX with 8 *N* chromic acid in acetone formed the hydroxyketone X,[13] which was later employed for the synthesis of the 17α-methyl compound. Longer oxidation gave the Δ^5-diketone XI, which has no selective ultraviolet absorption. Although isomerization of 3-oxo-Δ^5 steroids to the conjugated Δ^4 derivatives has been accomplished with mineral acid, alkali,[14,15] and oxalic acid,[16] only gummy mixtures or starting material were obtained when these procedures were applied to XI, possiby owing to the influence of the electronegative 19-nitrile function. It was found, however, that simple chromatography of XI on basic alumina produced XV; neutral alumina gave lower yields of XV, whereas acid alumina was ineffective. In agreement with findings on related compounds,[17] the presence of the 19-nitrile function in XV causes a hypsochromic shift of 10 mμ in the ultraviolet spectrum (λ_{max} 231 mμ). Selective reduction of androstenedione to testosterone with tri-*t*-butoxy lithium aluminum hydride has been reported,[18] but under similar conditions XV did not give the expected XVII. Instead, equal amounts of the Δ^4-diol XVI and what appeared to be impure 3β-hydroxy-17-oxoandrost-4-ene-19-nitrile were isolated by chromatography. The reversed reactivity of the keto groups at C-3 and C-17 may be due to the inductive or steric effect of the C-19 nitrile. Success was achieved in the preparation of XVII by complete reduction of XV with tri-*t*-butoxy lithium aluminum hydride to the allylic diol XVI, followed by selective oxidation with manganese dioxide.

The progesterone derivatives XX[19]–XXV were obtained by similar methods.

The 17α-methyl compounds were obtained by treatment of X with methylmagnesium bromide to furnish XII. Reduction of XII with lithium aluminum hydride stopped at the imine stage[2] and gave XIII after hydrolysis. Further reduction of XIII with sodium borohydride gave the triol XIV. Oxidation of XII and XIV gave, respectively, the methyl testosterone analogs XVIII and XIX.

(12) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

(13) Alternate syntheses of IX and X have been recorded in ref. 2. Compounds VIII and IX also have been obtained by a different sequence involving the Barton reaction by R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91**, 1420 (1961).

(14) *Cf.* C. Djerassi, R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936).

(16) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953).

(17) E. P. Oliveto, L. Weber, M. M. Pechet, and E. B. Hershberg, *ibid.*, **81**, 2833 (1959).

(18) J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(19) After our initial disclosure of compound XX in ref. 3c, its preparation was also recorded in ref. 8c.

TABLE I
ANDROGENIC–MYOTROPHIC ASSAY

Compound	Body wt. gain, g./rat	Ventral prostate wt., mg. Mean ± S.D.	Seminal vesicle wt., mg. Mean ± S.D.	Levator ani wt., mg. Mean ± S.D.	Activity (cf. testosterone propionate) Androgenic	Myotrophic
Series I						
Castrate control	34	14.5 ± 4.1	11.8 ± 2.1	29.7 ± 1.6		
Testosterone propionate 0.3 mg./rat	36	32.2 ± 12.3	17.5 ± 2.1	34.3 ± 2.0		
IX	29	13.1 ± 1.4	11.7 ± 0.6	25.0 ± 3.2	0	0
XV	31	13.1 ± 1.4	12.0 ± 0.5	25.9 ± 2.4	0	0
XVII	36	14.2 ± 3.7	15.1 ± 1.9	30.8 ± 2.4	<0.1	0
Series II						
Castrate control	31	12.1 ± 0.8	10.8 ± 0.8	25.0 ± 6.7		
Testosterone propionate 0.3 mg./rat	37	59.8 ± 10.0	39.7 ± 6.7	45.9 ± 5.0		
[a]	37	16.6 ± 1.1	12.6 ± 0.9	29.3 ± 3.0	<0.1	0
[b]	35	11.0 ± 0.9	9.3 ± 1.2	24.9 ± 4.0	0	0
XVIII	33	17.4 ± 2.6	10.3 ± 0.8	22.2 ± 2.2	0	0
XIII	41	26.7 ± 6.0	13.1 ± 2.3	34.2 ± 5.3	<0.1	<0.1
XIV	39	18.6 ± 3.7	11.2 ± 1.1	31.5 ± 3.2	<0.1	0

[a] 3β-Hydroxy-19-oximinoandrost-5-en-17-one. See ref. 2. [b] 19-Oxoandrost-5-ene-3β,17β-diol.[2]

TABLE II
ANTIANDROGENIC–ANTIMYOTROPHIC ASSAY

Compound	Body mean wt. gain, g./rat	Ventral prostate wt., mg. Mean ± S.D.	Seminal vesicle wt., mg. Mean ± S.D.	Levator ani wt., mg. Mean ± S.D.	Activity, % inhibition of response to TP at 10:1 dose level Androgenic	Myotrophic
Castrate	31	12.1 ± 0.8	10.8 ± 0.8	25.0 ± 6.7		
TP	37	59.8 ± 10.0	39.7 ± 6.7	45.9 ± 5.0		
XVII	37	59.5 ± 4.8	37.2 ± 4.4	49.4 ± 3.6	0	0
XVI	30	50.3 ± 12.6	34.5 ± 13.2	37.2 ± 5.3	0	42
VI	39	61.2 ± 5.7	39.6 ± 9.2	45.2 ± 5.8	0	0
XII	39	64.8 ± 4.4	45.5 ± 6.3	48.0 ± 2.3	0	0
[a]	38	68.9 ± 6.5	47.9 ± 4.3	55.6 ± 5.5	0	0
XIII	34	46.2 ± 5.3	29.1 ± 6.1	41.2 ± 6.9	37	0

[a] 19-Oxoandrost-5-ene-3β,17β-diol. See ref. 2.

Pharmacological Methods[20]

Androgenic—Myotrophic assay.[21]—The test materials (total dose 3.0 mg./rat) in carboxymethylcellulose (CMC) suspension were given by subcutaneous injection, once daily for 7 days, to groups of five castrate male rats 21 days of age at the start of the test. Autopsy was performed on the day following the last day of administration.

Antiandrogenic–Antimyotrophic Assay.[22]—The procedure was the same as the preceding assay, except that the test compound (total dose 3.0 mg./rat) and testosterone propionate (total dose 0.3 mg./rat) were administered concomitantly to the same animal at separate sites.

Progestational Assay.[23]—The test materials were given by subcutaneous injection for five days to groups of two estrogen-primed immature female rabbits. Autopsy was on the day following the last day of administration. Histological preparations made from sections of uterine tissue were examined microscopically to determine the degree of progestational response.

Statistical Analysis.—The significance of the data was established by the "t" test; the 95% confidence level was used as the limit of significance.

Discussion

The data in Tables I, II, and III are of particular interest in considering the hypothesis of Ringold[24] regarding the mode of adsorption of steroids on receptors: "The interaction of androgens with a cellular or enzymatic surface necessary to elicit a classical androgenic response is on the α-face (back side) of the androgen molecule, in contrast to progestational compounds, in which interaction must be with the β-face of the progestational agent in order for the steroid to exhibit its basic biological effect." Ringold has suggested that the ideal test situation would be the comparison of testosterone and progesterone analogs having bulky groups in the 10β-position; activity of the testosterone analogs and inactivity of the progesterone derivative would constitute strong evidence in favor of the hypothesis.

The compounds described in the present work are well suited to test the Ringold theory. Examination of

(20) Pharmacological tests were performed at The Endocrine Laboratories, Madison, Wisconsin.

(21) L. C. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

(22) *Cf.* L. O. Randall and J. J. Selitto, *Endocrinology*, **62**, 893 (1958).

(23) T. Miyake, "Methods in Hormone Research," Vol. 2, P. 1. Dorfman, Ed., Academic Press, New York, N. Y., 1962, p. 135.

(24) H. J. Ringold, in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Ed., Pergamon Press, New York, N. Y., 1961, pp. 200–232.

Table III

Progestational Assay

Compound, total dose/rabbit	Mean body wt., g./rabbit	Mean ovarian wt., mg.	Mean uterine wt., g.	Average response
Progesterone (0.2 mg.)	282	29.8	0.88	0.8+
XXV (2.0 mg.)	331	62.8	0.93	0.0

Courtauld models (Fig. 1) shows that the nitrile at the 10β-position of the steroid nucleus has a greater van der Waals radius in the plane perpendicular to the plane of the fused ring system than does a methyl group. On the basis of steric factors alone, therefore, the activity of testosterone-19-nitrile would be similar to that of testosterone itself, if α-adsorption were operative. Correspondingly, if β-adsorption is involved in the mechanism of action of progesterone at the molecular level, progesterone-19-nitrile should be less active than progesterone itself. It is also true, however, that the polarity of the nitrile group is quite different from that of the methyl group, the magnitude of this difference being strikingly demonstrated by the difference in the ultraviolet absorption maxima of testosterone (λ_{max} 240 mμ) and the corresponding 19-nitrile (λ_{max} 232 mμ). This introduction of a strongly electronegative group in the vicinity of the 3-ketone, therefore, must also be considered in assessing the activity of the steroidal nitriles. However, since the introduction of 4-chloro[25,26] and 6-fluoro[27] substituents into testosterone does not abolish androgenic action, the inductive effects of the nitrile function may be small in comparison to the steric effect on the biological activity of androgen analogs, although the 6-nitro testosterones exhibit neither androgenic nor myotrophic action.[28] Again, the high progestational action of the 6-halogenated progesterones,[29] in which the electronegative substituent is also one carbon removed from the double bond, allows a similar argument for the progestational agents.

The data in Tables I, II, and III indicate that none of the C-19 substituted testosterone analogs possess appreciable myotrophic or androgenic action. Moreover, progesterone-19-nitrile lacks progestational action. It is noteworthy, however, that XVI and XIII exhibit antimyotrophic and antiandrogenic action, respectively. This antagonistic effect apparently occurs at the tissue receptor sites, since the two compounds oppose the action of exogenous testosterone in castrate rats.

In considering these data in connection with the question of steroid–receptor interaction, it must first be pointed out that the Ringold hypothesis has as a basic premise that steroids which lack androgenic action do not interact with the appropriate receptor. That this is not necessarily the case is apparent from the numerous substances (*inter alia*, anticholinergics and antihistaminics) which are known to function by interacting with, and therefore blocking, the *same tissue receptors* utilized by the corresponding protagonist compound. It is quite reasonable, therefore, to hold that lack of androgenic action in a steroid only proves that the substance does not initiate the series of biochemical events which we call androgenic action, but that alone it yields no information regarding receptor binding. A second unstated premise underlying the α-absorption theory is that all steroid analogs reach the appropriate site of action. However, as Tomkins[30] has already remarked in this connection, it is difficult to say which chemical alterations affect local activity and which, for example, change localization and distribution.

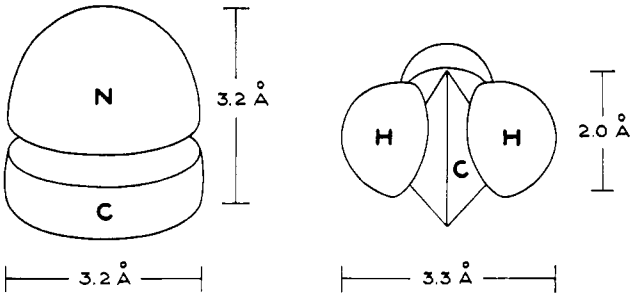


Fig. 1.—Relative sizes of methyl and nitrile groups as taken from Courtauld models.

The biological data are consistent with the hypothesis that both androgenic and myotrophic responses, like the progestational response, are initiated by the *β-face absorption* of a steroid on a tissue receptor. The low potency of the C-19 substituted steroids can thus be rationalized in terms of steric interference with drug–receptor fit, or with the inability of the modified compound to initiate the normal response. This conclusion is also in accord with the high androgenic and myotrophic potency of the 7α-methyltestosterone derivatives[31] in which the axial 7α-methyl group would presumably interfere with α-adsorption. The testosterone antagonists described in this study may be considered simply as blocking agents of the anticholinergic type. This antagonistic effect is also evidence that at least some of the C-19 modified compounds are reaching the site of action and that the lack of activity cannot be ascribed simply to changes in drug distribution.

In summary, although only tentative conclusions can be drawn from these studies in intact animals, the present data do not support the view that androgens, as distinct from other steroids, function *via* adsorption on the α-face.

Experimental[32]

5α-Chloroandrostane-3β,6β,17β-triol 3,17-Diacetate (I).—A mixture of 24.0 g. (0.064 mole) of androst-5-ene-3β,17β-diol diacetate, 750 ml. of ether, 60.0 g. of calcium hypochlorite, and 1800 ml. of water was treated with 45 ml. of glacial acetic acid and shaken vigorously for 30 min. After separation of the ether layer,

(25) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

(26) D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 1184 (1956).

(27) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(28) A. Bowers, M. Sánchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959).

(29) A. Bowers, L. C. Ibañez, and H. J. Ringold, *ibid.*, **81**, 5991 (1959).

(30) G. M. Tomkins, *ibid.*, **85**, 492 (1963).

(31) *Cf.* J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *Steroids*, **1**, 317 (1963), and references cited therein.

(32) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Infrared spectra were obtained with a Beckman IR-5 instrument. Ultraviolet spectra were obtained with a Cary Model 11 instrument. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, California. Optical rotations were obtained in a 0.5 dm. tube with a Rudolph photoelectric polarimeter. N.m.r. spectra were obtained at a field strength of 60 Mc./sec. on samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Resonance positions are reported in δ (p.p.m.) values where possible; unresolved humps are described in c.p.s. units (60 Mc./sec.). It is a pleasure to thank Mr. H. Rolewicz for large-scale preparation of intermediates.

the aqueous phase was extracted with 500 ml. of ether. The combined ether extract was washed successively with 300 ml. of 5% sodium bicarbonate solution and water and dried over sodium sulfate. Concentration of the solvent at 30° under reduced pressure, and digestion of the product with hot methanol gave, on cooling, 11.0 g. (40%) of colorless crystals, m.p. 199–201°. Recrystallization from methanol furnished the analytical sample, m.p. 200–201°; $[\alpha]^{25}D$ −43° (*c* 1% in $CHCl_3$): λ_{max}^{KBr} 2.90, 5.75, 5.82, and 8.00 μ.

Anal. Calcd. for $C_{23}H_{35}ClO_5$: C, 64.69; H, 8.26; Cl, 8.30. Found: C, 64.89; H, 8.24; Cl, 8.01.

5α-Chloro-*syn*-19-oximinoandrostane-3β,6β,17β-triol 3,17-Diacetate (III).—A solution of 10.0 g. (0.234 mole) of I in 45 ml. of pyridine was treated with nitrosyl chloride at 15–20° until a heavy precipitate of pyridine hydrochloride appeared and the solution became dark brown. The pyridine was removed by evaporation under reduced pressure at 25°, and the residue was rinsed with methanol into 300 ml. of ice water. The resulting precipitate was collected by filtration, washed with water, triturated with a small amount of cold methanol to remove colored impurities, and dried under vacuum at 25°. There was obtained 10.0 g. (94%) of the nitrite ester, m.p. 118–120°; λ_{max}^{KBr} 5.75, 6.05, 8.04, and 13.10 μ, which was too unstable to allow recrystallization.

Under an atmosphere of nitrogen, previously purified by passage through potassium pyrogallate solution, the foregoing nitrite, in 200 ml. of toluene, was irradiated for 2.5 hr. at 0° by means of an immersed 200-w. high pressure mercury arc equipped with a borosilicate filter. The course of the reaction was followed by periodic testing for unchanged nitrite ester. The presence of the nitrite ester was indicated by the appearance of a blue color upon the addition of a drop of the test solution (diphenylamine in concentrated sulfuric acid)[9] to 2 drops of the reaction solution and 1 drop of water. At the conclusion of the reaction, the precipitated 19-nitroso compound was filtered and washed with petroleum ether to afford 5.2 g. (52%) of 5α-chloro-19-nitrosoandrostane-3β,6β,17β-triol 3,17-diacetate, as a colorless dimer, m.p. 159–160°.

The dimer (5.2 g.) was refluxed in 250 ml. of 2-propanol for 1 hr. Evaporation of the solvent under reduced pressure gave 5.0 g. of III, m.p. 190–195°. It was recrystallized from aqueous ethanol to furnish 4.1 g. (41% over-all) of the product which had double melting points: 138–140°; 198–200°. The same sample recrystallized from acetone–hexane gave the analytical sample with a single m.p. 201–203°; $[\alpha]^{25}D$ −51° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.95, 5.74, 5.83, and 8.00 μ; $\lambda_{max}^{CHCl_3}$ 2.81 (sharp), 3.1–3.3 μ (broad); n.m.r. 0.73 (C-18 methyl), 2.02, 2.05 (acetate methyls), 4.04 (3α-H) 263–288 c.p.s. (17α-H), 300–340 c.p.s. (6α-H), 7.54 (C-19 H).

Anal. Calcd. for $C_{23}H_{34}ClNO_6$: C, 60.58; H, 7.51; Cl, 7.77; N, 3.02. Found: C, 60.44; H, 7.62; Cl, 7.99; N, 3.21.

5α-Chloro-*syn*-19-oximinocholestane-3β,6β-diol 3-Acetate (IV).—The nitrite ester derived from 15.0 g. of 5α-chlorocholestane-3β,6β-diol 3-acetate (II) was irradiated in a manner similar to that described for the preparation of III. The resulting 19-nitroso compound was heated under reflux in 2-propanol to give 5.2 g. (29%) of the oxime IV. The analytical sample, recrystallized from acetone–hexane, had m.p. 219–220°; $[\alpha]^{25}D$ −25° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.90, 5.75, and 8.07 μ; $\lambda_{max}^{CHCl_3}$ 2.82 (sharp), 3.1–3.3 μ (broad); n.m.r. (from 2 p.p.m. up) 2.00 (C-18 methyl), 230–247 (3α-H), 303–340 c.p.s. (6α-H), and 7.45 (19-H).

Anal. Calcd. for $C_{29}H_{48}ClNO_4$: C, 68.29; H, 9.48; Cl, 6.95; N, 2.74. Found: C, 68.38; H, 9.18; Cl, 7.19; N, 2.91.

19-Acetoxyimino-5α-chloroandrostane-3β,6β,17β-triol Triacetate (V).—A solution of 0.2 g. of III in 3 ml. of pyridine and 2 ml. of acetic anhydride was kept at 27° for 18 hr. It was poured into water to furnish 0.2 g. of precipitate which, on crystallization from methanol, gave the analytical sample, m.p. 158–159°; $[\alpha]^{25}D$ −45° (*c* 1% in $CHCl_3$).

Anal. Calcd. for $C_{25}H_{36}ClNO_8$: C, 60.04; H, 7.09; N, 2.59. Found: C, 59.92; H, 7.11; N, 2.71.

The oil obtained by fusion of this compound exhibited $\lambda_{max}^{CHCl_3}$ 4.50 (CN), 5.80, and 8.10 μ.

19-Oximinoandrost-5-ene-3β,17β-diol 3,17-Diacetate (VI).—To a solution of 10.0 g. (0.219 mole) of III in 100 ml. of glacial acetic acid heated to 85°, there was added 20.0 g. of zinc dust, and the mixture was stirred at 90–95° for 30 min. The reaction mixture was cooled, filtered, and the filtrate was poured slowly with stirring into 1 l. of water. After 2 hr. the product was filtered, washed with water, and dried to furnish 7.9 g. of crude material, which was recrystallized from aqueous ethanol to yield 6.9 g. (78%) of colorless crystals, m.p. 150–157°. Further recrystallization gave the analytical sample, m.p. 157–160°; $[\alpha]^{25}D$ −151° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.95, 5.75, and 8.00 μ; $\lambda_{max}^{CHCl_3}$ 2.81 (sharp) 5.80, 8.05; n.m.r. 0.76 (C-18 H), 260–295 (acetate methyls), 333–351 c.p.s. (6-H), and 7.35 (19-H).

Anal. Calcd. for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.68; H, 7.97; N, 3.11.

3β-Hydroxy-19-oximinocholest-5-ene Acetate (VII).—A solution of 1.5 g. of IV in 30 ml. of acetic acid was heated to 95° with 3.0 g. of zinc dust for 30 min. The product was isolated in a manner similar to that described for the preparation of VI. Recrystallization from aqueous ethanol gave the analytical sample m.p. 155–162°; $[\alpha]^{25}D$ −99° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 3.05, 5.75, and 8.00 μ; n.m.r. (from 2 p.p.m. up) 2.00 (C-18 methyl), 260–294 (3α-H), 330–347 c.p.s. (6-H), 7.34 (19-H), 484–530 c.p.s. (OH).

Anal. Calcd. for $C_{29}H_{47}NO_3$: C, 76.11; H, 10.35; N, 3.06. Found: C, 76.30; H, 10.45; N, 2.89.

3β,17β-Dihydroxyandrost-5-ene-19-nitrile Diacetate (VIII).—A solution of 6.8 g. (0.0176 mole) of VI in 70 ml. of acetic anhydride was refluxed for 2 hr. and poured into 500 ml. of cold water. After 1 hr., the precipitate was filtered and washed with water to afford 6.4 g. (98%) of crude product, m.p. 157–160°. Recrystallization from 70% ethanol gave the analytical sample, m.p. 162–163°; $[\alpha]^{25}D$ −167° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 4.50, 5.77, and 8.08 μ.

Anal. Calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.50; H, 7.95; N, 3.45.

3β,17β-Dihydroxyandrost-5-ene-19-nitrile (IX).—A solution of 6.4 g. (0.0166 mole) of VIII and 24.0 g. of potassium hydroxide in 300 ml. of methanol and 50 ml. of water was kept at 27° for 18 hr. and then concentrated to 100 ml. under reduced pressure. It was diluted with 200 ml. of water, and the resulting crystalline precipitate was filtered to give 4.9 g. (98%) of the product, m.p. 205–207°. Recrystallization from acetonitrile gave the analytical sample, m.p. 208–209°; $[\alpha]^{25}D$ −16° (*c* 1% in methanol); λ_{max}^{KBr} 2.93 and 4.50 μ.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.39; H, 9.05; N, 4.49.

3β-Hydroxy-17-oxoandrost-5-ene-19-nitrile (X).—A solution of 0.7 ml. of 8 *N* chromic acid reagent was rapidly added to a solution of 0.25 g. (0.00083 mole) of IX in 50 ml. of acetone at 13–15° under a nitrogen atmosphere. After 5 min. the excess oxidizing agent was destroyed with 2-propanol. The green sludge was removed by filtration. After the addition of 3 ml. of water, the filtrate was partially evaporated under reduced pressure. The steroid precipitate was filtered and washed well with water to afford 0.2 g. of a crude mixture which was indicated by thin layer chromatography (silica gel–ether) to contain mainly X, a small portion of XI, and a trace of the starting material. Chromatography on alkaline alumina gave 0.025 g. of XV, m.p. 182–184° (4% methanol in ether), and 0.13 g. (52%) of X (8% methanol in ether), m.p. 189–193°. The last product was recrystallized from acetone–hexane to give the analytical sample, m.p. 193–195°; $[\alpha]^{25}D$ −126° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.91, 4.5, and 5.75 μ.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.22; H, 8.20.

3,17-Dioxoandrost-5-ene-19-nitrile (XI).—A solution of 6.0 ml. of 8 *N* chromic acid reagent was added to a solution of 2.0 g. (0.00667 mole) of IX in 300 ml. of acetone at 15° under a nitrogen atmosphere; the mixture was maintained at 10–15° for 20 min. Excess oxidizing reagent was destroyed by the addition of 2-propanol, and the green precipitate was removed by filtration. The acetone filtrate was evaporated under reduced pressure after the addition of 20 ml. of water. The precipitated steroid was filtered and washed with water to afford 1.6 g. (80%) of the crude Δ^5 diketone (XI), m.p. 150–158°, which contained 5% of the Δ^4 isomer (XV) (calculated from the ultraviolet absorption at 231 mμ). It was recrystallized from acetone–hexane to give the analytical sample, m.p. 158–164°; $[\alpha]^{25}D$ −70° (1% in $CHCl_3$); λ_{max}^{KBr} 4.50 and 5.80 μ.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.44; H, 7.86.

17α-Methylandrost-5-ene-3β,17β-diol-19-nitrile (XII).—To a solution of 4.0 g. (0.0134 mole) of X in 50 ml. of anhydrous tetrahydrofuran and 100 ml. of anhydrous ether there was slowly added 100 ml. of an ethereal solution of methylmagnesium bromide (3 *M* solution, Arapahoe Chemicals, Inc., Boulder, Colorado). After refluxing for 10 hr., the reaction mixture was poured into

ice and was acidified with 20% hydrochloric acid to pH 1. It was extracted with 3 portions of tetrahydrofuran–ether (2:10), and the combined extract was washed with water until the washings were neutral. After drying over sodium sulfate the solvent was evaporated to afford 3.9 g. of residue. Recrystallization from acetone–hexane furnished 2.8 g. (67%) of XII as fine needles, m.p. 211–215°. The analytical sample had m.p. 214–216°; $[\alpha]^{25}D$ −171° (*c* 1% in MeOH); λ_{max}^{KBr} 2.83 (sharp), 3.06 (broad), and 4.50 μ.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27. Found: C, 76.37; H, 9.34.

17α-Methyl-19-oxoandrost-5-ene-3β,17β-diol (XIII).—A stirred suspension of 1.35 g. (0.00428 mole) of XII and 0.8 g. of powdered lithium aluminum hydride in 300 ml. of anhydrous tetrahydrofuran was heated under reflux for 120 hr. The excess hydride was decomposed with ethyl acetate under ice-bath cooling. This mixture was acidified with 20% hydrochloric acid to pH < 1, and was stirred for 8 hr. until a clear solution resulted (if not, more acid is needed to acidify the solution). The mixture was extracted with several portions of ether and the ether extract was washed with water until the washings were neutral. After drying over sodium sulfate, the solvent was evaporated under reduced pressure to afford 0.8 g. (59%) of the crude product, m.p. 195–203°. The analytical sample, recrystallized from acetone–hexane, had m.p. 202–207°; $[\alpha]^{27}D$ −253°; λ_{max}^{KBr} 3.02 (broad), 3.74 (weak), and 5.75 μ (no CN band).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.21; H, 9.28.

17α-Methylandrost-5-ene-3β,17β,19-triol (XIV).—A solution of 0.5 g. (0.00157 mole) of XIII and 0.5 g. of sodium borohydride in 50 ml. of methanol was maintained at 25° for 2 hr. The mixture was acidified with 5% hydrochloric acid and extracted with ether. The ether extract was washed with water until neutral and dried (sodium sulfate). Evaporation of the solvent afforded 0.45 g. (90%) of the crude product, m.p. 230–233°. Recrystallization from acetone–hexane gave the analytical sample, m.p. 232–233°; $[\alpha]^{25}D$ −61° (*c* 0.5% in MeOH); λ_{max}^{KBr} 3.00 μ, no C=O band.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.70; H, 10.14.

3,17-Dioxoandrost-4-ene-19-nitrile (XV).—Crude XI (1.5 g.) was chromatographed on alkaline alumina whereupon it isomerized to the Δ^4 diketone. From the 4% methanol in ether fractions there was obtained 0.9 g. (60%) of the product, m.p. 182–184°. Recrystallization from acetone–hexane gave the analytical sample, m.p. 184–185°; $[\alpha]^{25}D$ +251° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 4.50, 5.75, 5.95, and 6.14 μ; λ_{max}^{EtOH} 231 μ (ε 16,000).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.94; H, 7.74.

3β,17β-Dihydroxyandrost-4-ene-19-nitrile (XVI).—A solution of 0.7 g. (0.00235 mole) of XV and 2.5 g. (0.0091 mole) of LiAl(*t*-BuO)$_3$H in 50 ml. of tetrahydrofuran was maintained at 0° for 45 min. After the addition of 100 ml. of 5% acetic acid, the product was extracted with ether, and the ether extract was washed with 5% sodium bicarbonate solution and water and dried over sodium sulfate. Evaporation of the solvent gave 0.6 g. (86%) of colorless crystals, m.p. 247–249°. Recrystallization from acetone–hexane gave the analytical sample, m.p. 248–249°; $[\alpha]^{25}D$ +106° (*c* 1% in methanol); λ_{max}^{KBr} 2.91, 3.02, and 4.50 μ.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03. Found: C, 75.68; H, 9.15.

17β-Hydroxy-3-oxoandrost-4-ene-19-nitrile (XVII).—A solution of 0.3 g. (0.001 mole) of XV in 50 ml. of tetrahydrofuran was stirred with 1.5 g. of manganese dioxide at 25° for 10 hr. The manganese dioxide was removed by filtration and washed with acetone. The residue from evaporation of the filtrate was crystallized from aqueous ethanol to furnish 0.25 g. (83%) of crystals, m.p. 186–189°. Further recrystallization gave the analytical sample, m.p. 189–190°; $[\alpha]^{25}D$ +178° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 3.06, 4.50, 5.97, and 6.14 μ; λ_{max}^{EtOH} 232 mμ (ε 14,500).

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 75.95; H, 8.58.

17α-Methyl-17β-hydroxy-3-oxoandrost-4-ene-19-nitrile (XVIII).—A solution of 0.5 g. (0.00159 mole) of XII in 100 ml. of acetone was treated with 0.75 ml. of 8 *N* chromic acid reagent as described in the preparation of 3,17-dioxoandrost-4-ene-19-nitrile. The crude material was chromatographed on alkaline alumina to give 0.28 g. (56%) of XVIII, m.p. 192–193° (from fractions of 2% methanol–ether). The analytical sample, recrystallized from acetone–hexane, had m.p. 193–194°; $[\alpha]^{25}D$ +145° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.95, 4.50, 6.00, and 6.16 μ; λ_{max}^{EtOH} 232 mμ (ε 15,500).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.43; H, 8.58.

3-Oxo-17α-methylandrost-4-ene-17β,19-diol (XIX).—A mixture of 10 ml. of cyclohexanone and 15 ml. of toluene was heated to boiling and 4 ml. of distillate was collected and discarded. Then 0.35 g. (0.0011 mole) of XIV was quickly dissolved in the hot anhydrous solution and 1.0 g. of powdered redistilled aluminum isopropoxide was added. The mixture quickly was brought to reflux and maintained there for 10 min. The mixed solvent was removed *in vacuo* at 70–75°, and the residue was taken up in 200 ml. of chloroform which was washed with *N* sulfuric acid (100 ml.) and water, and dried over sodium sulfate. Evaporation of the chloroform left a sirupy residue containing some cyclohexanone. The residue was chromatographed on 10.0 g. of neutral alumina; the following eluents were used: four 5-ml. portions of ether; four 5-ml. portions of methanol–ether (1%); four 5-ml. portions of methanol–ether (2%); four 5-ml. portions of methanol–ether (4%); four 5-ml. portions of methanol–ether (8%); four 5-ml. portions of methanol–ether (61%); and four 5-ml. portions of methanol–ether (32%). There was obtained (from fractions of 8% methanol–ether) 0.15 g. (43%) of XIX, m.p. 190–192°, and (from 16% methanol–ether) a trace of the starting material (identified by m.m.p.). The analytical sample of XIX, recrystallized from acetone–hexane, had m.p. 195–196°; $[\alpha]^{25}D$ +66° (*c* 0.5% in $CHCl_3$); λ_{max}^{KBr} 2.98, 6.02, and 6.15 (shoulder) μ; λ_{max}^{EtOH} 243 mμ (ε 14,100).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.64; H, 9.15.

5α-Chloro-3β,6β-dihydroxypregnan-20-one 3-Acetate (XX).—This compound was obtained from 24.0 g. of pregnenolone acetate by a procedure similar to that used for the preparation of I. Crystallization of the crude product from aqueous ethanol gave 10.8 g. (39%) of colorless crystals, m.p. 203–206°. Further recrystallization gave the analytical sample, m.p. 206–207° (inserted at 200°); $[\alpha]^{25}D$ +26° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.98 5.75, 5.88, and 8.13 μ; lit.[9] m.p. 196–197°, $[\alpha]^{CHCl_3}D$ 25.5°.

Anal. Calcd. for $C_{23}H_{35}ClO_4$: C, 67.20; H, 8.58. Found: C, 66.91; H, 8.54.

19-Oximino-5α-chloro-3β,6β-dihydroxypregnan-20-one 3-Acetate (XXI).—A solution of 7.0 g. (0.0159 mole) of the nitrite derived from XX in 200 ml. of toluene was irradiated for 2.0 hr. at 0°. The fine precipitate of the insoluble 19-nitroso compound which formed during the photolysis was filtered and washed with petroleum ether to afford 4.0 g. (57%) of nitroso compound. No exact melting point was observed owing to gradual isomerization to the high melting oxime on heating.

The crude nitroso compound was refluxed in 300 ml. of 2-propanol for 1 hr. The residue obtained from evaporation of the solvent was recrystallized from acetonitrile to furnish 3.1 g. (44%) of product, m.p. 223–226° (inserted at 220°). Further recrystallization gave the analytical sample, m.p. 230–231°; $[\alpha]^{25}D$ +16° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 2.91, 5.86, and 8.09 μ.

Anal. Calcd. for $C_{23}H_{34}ClNO_5$: C, 62.77; H, 7.78; N, 3.18. Found: C, 62.83; H, 7.91; N, 3.58.

3β-Hydroxy-19-oximinopregn-5-ene-20-one 3-Acetate (XXII).—A solution of 2.5 g. (0.00568 mole) of XXI in 50 ml. of glacial acetic acid (preheated to 85°) was treated with 5.0 g. of zinc dust in a manner similar to that described for the preparation of VI. There was obtained 2.0 g. of crude product, m.p. 153–158°, which was recrystallized from aqueous methanol to yield 1.7 g. (78%) of XXII, m.p. 160–165° (inserted at 150°); $[\alpha]^{25}D$ −71° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 3.04, 5.78, and 5.90 μ.

Anal. Calcd. for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58. Found: C, 71.19; H, 8.79.

Pregn-5-en-3β-ol-20-one-19-nitrile Acetate (XXIII).—A solution of 1.65 g. (0.00426 mole) of XXII in 30 ml. of acetic anhydride was refluxed for 2 hr. and poured into 300 ml. of water. The precipitate was filtered to afford 1.5 g. (92%) of product, m.p. 140–142°. Recrystallization from aqueous methanol gave the analytical sample, m.p. 145–146°; $[\alpha]^{25}D$ −92° (*c* 1% in $CHCl_3$); λ_{max}^{KBr} 4.50, 5.80, and 7.98 μ.

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46. Found: C, 74.61; H, 8.74.

Pregn-5-en-3β-ol-20-one-19-nitrile (XXIV).—A solution of 1.3 g. (0.0398 mole) of XXIII and 4.5 g. of potassium hydroxide in 80 ml. of methanol and 10 ml. of water was kept at 27° for 81 hr. The solvent was concentrated and poured into water to

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); $\lambda_{max}^{CHCl_3}$ 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}^{KBr} 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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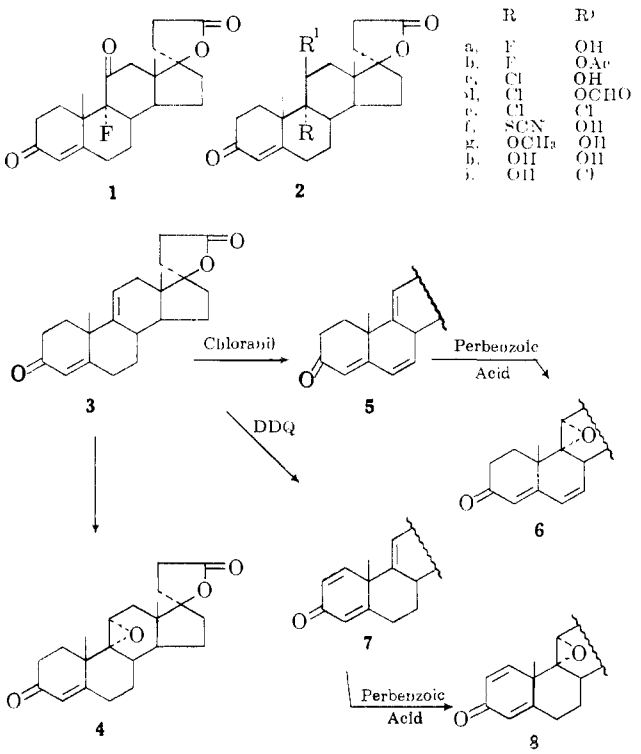
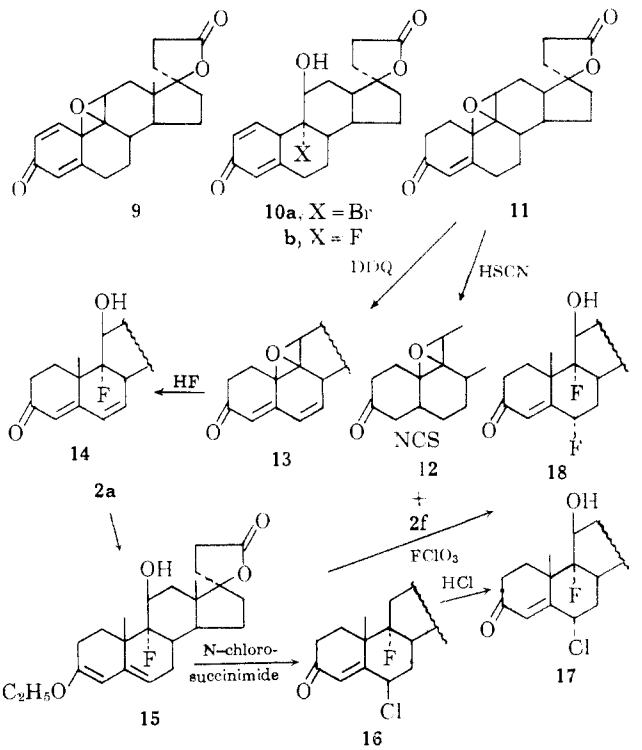
A number of steroidal 17-spirolactones bearing substituents at positions 9 and 11 have been prepared. The syntheses and biological activities are described.

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. Muir, and J. A. Cella, *ibid.*, **25**, 90 (1960).

(2) K. Takeda and T. Komeno, *Chem. Pharm. Bull.* (Tokyo), **8**, 468 (1960).