extraction with methylene chloride (4 × 250 ml.), the combined extracts were washed 15 times with 200 ml. of water. The resultant solution was dried over sodium sulfate and evaporated to dryness. The residue upon crystallization from ether–hexane gave 3.5 g. of crystals, m.p. 195–200°. Five recrystallizations from methanol led to the pure sample, m.p. 209–210°, $[\alpha]D$ +20°, λ_{max}^{EtOH} 338–340 mμ, log ε 4.18, λ_{max}^{KBr} 3.02, 6.17 and 6.51 μ.

Anal. Calcd. for $C_{27}H_{46}N_2O_2$: C, 75.30; H, 10.77; N, 6.51. Found: C, 75.06; H, 10.80; N, 6.33.

2-(2′-N,N-Diethylaminoethylaminomethylene)-5α-androstane-17β-ol-3-one 17-Acetate (VIc).—By treatment of 2-hydroxymethylene-5α-androstane-17β-ol-3-one 17-acetate[19] as described for the preparation of Vc, there was obtained pure VIc after recrystallization from hexane, m.p. 122–123°, $[\alpha]D$ +44°, λ_{max}^{EtOH} 328–330 mμ, log ε 4.33.

Anal. Calcd. for $C_{28}H_{46}N_2O_3$: C, 73.32; H, 10.11; N, 6.11; O, 10.47. Found: C, 73.28; H, 10.39; N, 6.06; O, 10.74.

2-(N-Piperidylmethylene)-17α-methyl-5α-androstane-17β-ol-3-one (Vd).—To 20 ml. of dry benzene and 1.0 g. of Ib was added 1.0 ml. of piperidine. The solution was then heated on a steam bath and after 10 min. all of the benzene was evaporated. Crystallization of the residue from benzene gave 980 mg. of crystals, m.p. 230–235°, raised by 4 recrystallizations from the same solvent to m.p. 242–244°, $[\alpha]D$ −255°, λ_{max}^{EtOH} 334 mμ, log ε 4.37, λ_{max}^{KBr} 3.08, 6.15 and 6.65 μ; lit.[19] m.p. 232–239°, $[\alpha]D$ −266.8°, λ_{max}^{EtOH} 333 mμ, ε 21,100.

Anal. Calcd. for $C_{26}H_{41}NO_2$: C, 78.14; H, 10.34; N, 3.51; O, 8.01. Found: C, 78.58; H, 10.36; N, 3.45; O, 7.98.

2-(N-Piperidylmethylene)-5α-androstane-17β-ol-3-one (VIb).—Starting from Ia, this substance was prepared in the same manner as Vd. It was recrystallized from acetone and had m.p. 219–221°, $[\alpha]D$ −256°, λ_{max}^{EtOH} 334–336 mμ, log ε 4.31.

Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.20; N, 3.63; O, 8.30. Found: C, 78.17; H, 10.42; N, 3.89; O, 8.10.

2-(2′-N,N-Dimethylaminomethylene)-17α-methyl-5α-androstane-17β-ol-3-one (Ve).—Dioxane (20 ml.) containing 1.0 g. of Ib, 2.5 g. of dimethylamine hydrochloride and 2.5 g. of sodium bicarbonate was stirred for 32 hr. at room temperature. After evaporation of the solvent, water (50 ml.) was added and the aqueous mixture was filtered. The collected precipitate was recrystallized once from methylene chloride–hexane and 3 times from methylene chloride–acetone to give *ca.* 400 mg. of crystals, m.p. 229–231°, $[\alpha]D$ −259°, λ_{max}^{EtOH} 334 mμ, log ε 4.25, λ_{max}^{KBr} 2.92 μ, 6.08 μ, and 6.48 μ.

Anal. Calcd. for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90; O, 8.90. Found: C, 76.41; H, 10.24; N, 3.81; O, 8.80.

2-(2′-N,N-Diethylaminomethylene)-17α-methyl-5α-androstane-17β-ol-3-one (Vf).—One gram of Ib was heated at reflux temperature in 50 ml. of benzene and 1 ml. of diethylamine. After 15 hr. the solution was concentrated to dryness and the residue was crystallized from ethyl acetate. By these means, 700 mg. of crystals was obtained, m.p. 180–181°. A single recrystallization from the same solvent gave Vf, m.p. 181–182°, $[\alpha]D$ −191°, λ_{max}^{EtOH} 334–336 mμ, log ε 4.30, λ_{max}^{KBr} 3.01, 6.16 and 6.60 μ.

Anal. Calcd. for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.67; N, 3.61; O, 8.26. Found: C, 77.18; H, 10.77; N, 3.72; O, 8.11.

2-(N-Methylanilinomethylene)-17α-methyl-5α-androstane-17β-ol-3-one (Vg).—Methanol (600 ml.) containing 30 g. of Ib and 30 ml. of N-methylaniline was heated on a steam bath for 2 hr. and then evaporated to dryness. The residue was chromatographed on 600 g. of neutral alumina whence hexane elution removed most of the unreacted N-methylaniline. Further elution with ethyl acetate–benzene (1:1) then gave solids which were recrystallized from acetone to yield 23.1 g. of crystals, m.p. 196–198°. A single recrystallization from the same solvent provided the pure sample, m.p. 198–199°, $[\alpha]D$ −417° (pyridine), λ_{max}^{EtOH} 238 and 346–348 mμ, log ε 3.64 and 4.30, λ_{max}^{KBr} 2.94, 6.06 and 6.49 μ.

Anal. Calcd. for $C_{28}H_{39}NO_2$: C, 79.76; H, 9.32; N, 3.32; O, 7.59. Found: C, 79.43; H, 9.14; N, 3.64; O, 7.99.

2-(*p*-Chlorophenylthiomethylene)-17α-methyl-androstane-17β-ol-3-one (Vi).—Dioxane (25 ml.) containing 1.0 g. of Ib, 1.0 g. of *p*-chlorothiophenol, and 50 mg. of *p*-toluenesulfonic acid monohydrate was heated on a steam bath for 1 hr., then poured into water (100 ml.). After extraction with ethyl acetate (5 × 40 ml.), the extracts were washed with cold 10% aqueous potassium hydroxide (2 × 30 ml.) and then with water until neutral. The solvent was dried and evaporated to leave a residue which upon crystallization from acetone–hexane gave 650 mg. of crystals, m.p. 163–165°. Three recrystallizations from acetone raised this melting point to 205–208°, $[\alpha]D$ +62°, λ_{max}^{EtOH} 258 and 323 mμ, log ε 3.60 and 4.07 λ_{max}^{KBr} 2.92, 6.02 and 6.52 μ.

Anal. Calcd. for $C_{27}H_{35}ClO_2S$: Cl, 7.72; S, 6.98. Found: Cl, 7.91; S, 7.20.

Acknowledgment.—We are indebted to Dr. R. I. Dorfman of the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and Dr. E. Shipley of the Endocrine Labs, Madison, Wisconsin, for the bioassays reported. For the recording and interpretation of the n.m.r. data, we gratefully acknowledge the service of Dr. Norman Bhacca, Varian Associates, Palo Alto, California.

Steroids. CCXIII.[1] Synthesis of Some 6-Chlorotestosterone Derivatives

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Received September 28, 1962

The syntheses of 6α- and 6β-chlorotestosterone acetate are described. Attempts to prepare 6α-chloro-17α-methyltestosterone resulted in a Wagner–Meerwein rearrangement. Nuclear magnetic resonance spectral studies support the structural assignments. 6α-Chlorotestosterone shows a favorable separation of anabolic and androgenic activities.

Although the preparations of 6-fluoro-[2] and 6-bromotestosterones[3] have been reported, the synthesis of the 6-chloro analogs has so far not been described.[4,5] Syntheses of testosterones bearing a 6α- and 6β-chloro substituent were undertaken therefore, in view of the established enhancement of biological activity due to the introduction of a halogen at position 6- of the steroid nucleus.[2,3,6]

The enol ether of testosterone acetate (Ia)[7] was converted through the agency of N-chlorosuccinimide in

(1) Steroids CCXII, R. I. Dorfman and F. A. Kinel, *Acta Endocrin.*, in press.

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

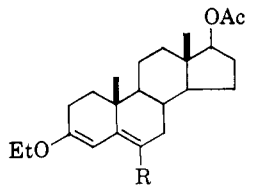
(3) Ch. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946); C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(4) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *ibid.*, **80**, 1216 (1958), have recorded the optical rotatory dispersion data for the 6β-chlorotestosterone prepared in the Syntex laboratories.

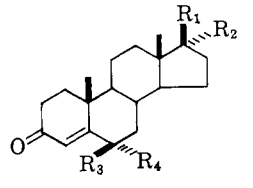
(5) After this paper was first submitted to the Editor a patent issued [A. Ercoli, U. S. Patent 3,053,735 (1962)] in which several other chlorotestosterone analogs are described.

acetone into 6β-chlorotestosterone acetate (IIa). Treatment of the latter with ethyl orthoformate and *p*-toluenesulfonic acid led to the 6-chloro enol ether (Ib) which was subjected to the action of hydrogen chloride in acetic acid giving the epimer, 6α-chlorotestosterone acetate (IIb).

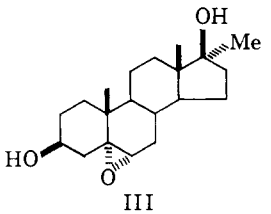
To arrive at the 17α-methyl-6-chlorotestosterones, 17α-methyl-androst-5-ene-3β,17β-diol was converted to the corresponding 5α,6α-epoxide (III)[8] and thence by treatment with pyridine hydrochloride–ethanol[9] to the derived chlorohydrin (IVa). Oxidation of the



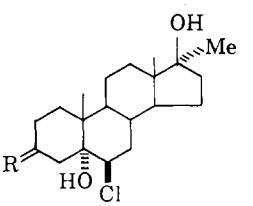
Ia, R = H
b, R = Cl



IIa, R = OAc, R_2 = R_4 = H, R_3 = Cl
b, R = OAc, R_2 = R_3 = H, R_4 = Cl
c, R = OH, R_2 = Me, R_3 = Cl, R_4 = H
d, R = OH, R_2 = Me, R_3 = H, R_4 = Cl



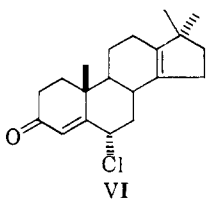
III



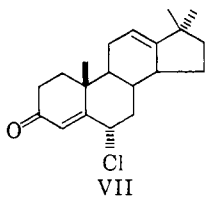
IV, R = αH, βOH
V, R = =O

latter by the Sarett reagent[10] yielded 6β-chloro-5α,-17β-dihydroxy-17α-methylandrostan-3-one (V). However, dehydration of the chlorohydrin (V) under the C_6-epimerizing conditions of acetic acid–hydrogen chloride[8] effected a Wagner–Meerwein rearrangement. Departure of the protonated 17β-hydroxyl generates a carbonium ion which collapses by migration of the 13-methyl group to the 17-position and loss of the 14α-proton, with formation of the 18-norandrost-13-ene VI. Evidence for the 6α-orientation of the chlorine stems from the ultraviolet spectrum (λ_{max}. 234 mμ).[11,12]

A nuclear magnetic resonance (n.m.r.) spectral study of the rearrangement product strikingly supports the proposed structure VI.[13] Singlets, each equivalent to 3-protons, assignable to the 13β- and 17α-methyl groups, occur at 52 c.p.s. and 91 c.p.s. in the n.m.r. spectrum of the precursor V. However after acid-catalyzed rearrangement both of these are absent and, instead, a new singlet equivalent to 6 protons appears at 59.3 c.p.s., attributable to two magnetically equivalent methyls as in VI, each experiencing some deshielding by virtue of its stereochemical relation to the Δ^{13}-double bond. Furthermore, at low fields, the vinylic proton resonance area and frequency remain virtually unchanged in IIb and VI, indicating the presence of only one vinylic proton (at C_4) in both compounds, and thus excluding as a possible structure for the rearrangement product the double bond isomer VII.[14]



VI



VII

Other noteworthy features of the n.m.r. spectrum of the rearrangement product VI are the resonances assigned to the C_4 olefinic proton and to the 6β-proton. The former proton resonance appears at 384 c.p.s. as a well-resolved doublet, $J_{H_4\ H_{6\beta}}$ 2.0 c.p.s. due to long-range coupling with the 6β-proton. An 8-line pattern, centered at 285 c.p.s., is interpreted by first order analysis as being due to coupling of the 6β-proton with the 4-proton, $J_{H_4\ H_{6\beta}}$ 2.0 c.p.s., the 7β-proton, $J_{H_{6\beta}\ H_{7\beta}}$ 5.3 c.p.s., and the 7α-proton, $J_{H_{6\beta}\ H_{7\alpha}}$ 12.2 c.p.s.[15]

Levisalles and his co-workers have reported additional chemical shifts, away from tetramethylsilane reference, of 15 c.p.s. for the 19-protons of both 6β-chloro- and 6β-bromocholestan-3-ones as compared with cholestan-3-one.[17] In a general study of steroid n.m.r. spectra, 6α- and 6β-halo-3-ketones and Δ^4-3-ketones of the androstane, pregnane, and corticoid series have been examined by us.[18] Thus it has been observed for Δ^4-3-ketones that 6α-fluoro and 6α-chloro

(6) (a) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 4423 (1958), (b) H. J. Ringold, E. Batres, A. Bowers, J. A. Edwards and J. Zderic, *ibid.*, **81**, 3485 (1959); (c) J. S. Mills, O. Candiani and C. Djerassi, *J. Org. Chem.*, **25**, 1056 (1960); (d) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson and J. A. Campbell, *Chem. and Ind.*, 1002 (1958); (e) J. S. Mills, A. Bowers, C. Casas Campillo, C. Djerassi and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 1264 (1959); (f) J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.*, **87** (1959); (g) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959); (h) A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *ibid.*, **7**, 153 (1959); (i) J. A. Edwards, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3156 (1959); (j) W. P. Schneider, F. H. Lincoln, G. B. Spero, H. C. Murray and J. L. Thompson, *ibid.*, **81**, 3167 (1959); (k) S. Karaday and M. Sletzinger, *Chem. and Ind.*, 1159 (1959); (l) A. Bowers, L. C. Ibáñez and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5991 (1959); (m) A. Bowers, *ibid.*, **81**, 4107 (1959); (n) J. S. Mills, A. Bowers, C. Djerassi and H. J. Ringold, *ibid.*, **82**, 3399 (1960); (o) H. J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, H. Martínez, E. Necoechea, J. Edwards, M. Velasco, C. Casas Campillo and R. I. Dorfman, *ibid.*, **80**, 6464 (1958); (p) J. A. Edwards, H. J. Ringold and C. Djerassi, *ibid.*, **82**, 2318 (1960).

(7) A. Serini and H. Köster, *Ber.*, **71**, 1766 (1938).

(8) S. A. Julia and H. Heusser, *Helv. Chim. Acta*, **35**, 2080 (1952).

(9) P. N. Chakravarty and R. H. Levin, *J. Am. Chem. Soc.*, **64**, 2317 (1942).

(10) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(11) For a detailed comparative study of the ultraviolet spectral absorption of 6α- and 6β-halosteroids, see A. Bowers and H. J. Ringold, *Experientia*, **17**, 65 (1961).

(12) Mild perchloric acid-catalyzed dehydration (non-epimerizing conditions) led to an unstable crystalline compound which was thought to be 6β-chloro-17α-methyltestosterone (IIc), m.p. 175–180°. The ultraviolet absorption maximum at 239 mμ supported a 6β-orientation of the chlorine substituent. However, Ercoli reports[5] m.p. 156° dec. for 6β-chloro-17α-methyltestosterone, and states that treatment of this compound with anhydrous chloroform–hydrogen chloride at 0° leads to the 6α-epimer IId, m.p. 153–154° dec. Ultraviolet data are not given. Our unstable product was not investigated further.

(13) N.m.r. spectra were taken in carbon tetrachloride or purified chloroform solution at 60 Mc. with a Varian A-60 spectrometer. Resonances are quoted as c.p.s. relative to a tetramethylsilane internal reference standard. A.D.C. thanks Prof. A. Sandoval and the Universidad Nacional Autónoma de México for time on the A-60 spectrometer. Accuracy limits are *ca.* ±1 c.p.s. for the chemical shift, δ, and *ca.* ±0.3 c.p.s. for coupling constants, *J*.

(14) Similar arguments have been presented recently in developing the structure of the Wagner–Meerwein rearrangement product of a different 17α-methylandrostan-17β-ol. See *Varian Tech. Info. Bull.*, **3**, No. 2 (1961), and V. Tortorella, G. Lucente and A. Romeo, *Ann. Chem.*, **50**, 1198 (1960).

(15) This analysis is based on the fact that for an axial proton on a cyclohexane ring $J_{trans} > J_{cis}$ for coupling with the protons of adjacent methylene.[1]

(16) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, pp. 84–86.

(17) J. Jacquesy, J. Lehn and J. Levisalles, *Bull. soc. chim. France*, 2444 (1961).

substituents cause only a small downfield shift (1–2 c.p.s.) of the 19-proton frequency, whereas for the 6β-fluoro group the shift is 6–7 c.p.s. and for the 6β-chloro group 15–16 c.p.s., downfield from tetramethylsilane (for a 60 Mc. oscillator frequency). Using these additive values[19] for the deshielding contributions of chlorine it can be seen (Table I) that the calculated and observed values of 19-proton resonance frequencies are in excellent agreement with structures IIa and VI.[20]

TABLE I

19-ANGULAR-METHYL PROTON N.M.R. FREQUENCIES

Steroid	Substituent 6α	Substituent 6β	C-19-proton resonance frequency, c.p.s. Observed	Calculated
Δ⁴-3-ketone	H	H	72.0[21]	71.0[19]
IIa	H	Cl	87.4	87.5
VI	Cl	H	71.9	72.0

Biological Activities.—In preliminary assays, only the 6α-chlorotestosterone acetate (IIb) showed a favorable anabolic-androgenic ratio. Assays[22,23] were carried out on the immature castrate rat. The effect on the weight of the seminal vesicle and ventral prostate was taken as a measure of androgenicity and the effect on the levator ani muscle gave the myotrophic (anabolic) activity. By injection, the 6α- and 6β-chloro epimers (IIa and IIb, respectively) showed approximately 0.8 and 0.2 times the androgenicity and approximately 3.0 and 0.2 times the anabolic activity of testosterone, respectively.

Experimental[24]

6β-Chlorotestosterone Acetate (IIa).—To a stirred ice-cold solution of the ethyl enol ether (Ia) of testosterone acetate (40.5 g.) in acetone (2 l.), and sodium acetate (24.0 g.) in water (240 ml.) were added, slowly, N-chlorosuccinimide (18.22 g.) and acetic acid (22 ml.). After 1.25 hr. stirring was discontinued, the whole diluted with water, and extracted with benzene. Following washes with water, bicarbonate solution, and again water, the solution was passed through an alumina column eluting with benzene, whereupon by evaporation, 6β-chlorotestosterone acetate was obtained (24.6 g.). Crystallization from acetone–hexane gave an analytical sample, m.p. 156–157°, $[\alpha]_D$ +3°, λ_{max} 240 mμ, log ε 4.16; ν_{max}^{KBr} 1732 and 1255 cm.$^{-1}$ (acetate), and 1680 and 1616 cm.$^{-1}$ (conjugated ketone).

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.12; H, 8.01; O, 13.10; Cl, 9.77. Found: C, 69.44; H, 8.15; O, 12.71; Cl, 9.89.

6-Chloro-3-ethoxy-17β-hydroxyandrosta-3,5-diene Acetate (Ib).—To 6β-chlorotestosterone acetate (500 mg.) in dry dioxane (3.7 ml.) were added ethyl orthoformate (0.5 ml.) and *p*-toluenesulfonic acid (30 mg.) and the whole was stirred during 2.5 hr. at room temperature. When the mixture was poured into water crystals separated which were collected, washed with water, and dried (520 mg.). Several recrystallizations from methanol afforded (Ib) as prisms, m.p. 143–144°, $[\alpha]_D$ −136°, λ_{max} 252 mμ, log ε 4.33; ν_{max}^{KBr} 1735, 1645, 1618, and 1248 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}ClO_3$: C, 70.40; H, 8.46; O, 12.22; Cl, 9.02. Found: C, 70.61; H, 8.64; O, 12.22; Cl, 9.02.

6α-Chlorotestosterone Acetate (IIb).—The dienol ether (Ig) (1 g.), acetic acid (15 ml.), and 20% hydrochloric acid (0.44 ml.) were kept together (1.5 hr.) at room temperature, then poured onto ice-water. Filtration yielded IIb (800 mg.) which, after a thorough washing with water, was recrystallized several times from acetone–hexane. The purified product (500 mg.) had m.p. 157–158°, and 145–151° on admixture with IIa, $[\alpha]_D$ +69°, λ_{max} 236 mμ, log ε 4.14; ν_{max}^{KBr} 1733, 1255, 1682 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.12; H, 8.01; O, 13.10; Cl, 9.77. Found: C, 68.84; H, 8.04; O, 13.02; Cl, 9.76.

6β-Chloro-5α,17β-dihydroxy-17α-methylandrostan-3-one (V).—5α,6α-Epoxy-17α-methylandrostan-3β,17β-diol[8] (III, m.p. 252–254°, $[\alpha]_D$ −85.8°, 7.8 g.), prepared from the action of monoperphthalic acid upon 17α-methyl-androst-5-ene-3β,17β-diol, was treated with pyridine hydrochloride (15 g.) in absolute ethanol (125 ml.) at reflux (2 hr.). Part of the ethanol (80 ml.) was removed by distillation and the remaining solution poured into ice-water. Filtration afforded the chlorohydrin (IV) (5.6 g.), further crystallized from acetone to m.p. 191–192°, $[\alpha]_D$ −62° (in pyridine), ν_{max}^{KBr} 3440 and 3380 cm.$^{-1}$.

A solution of the triol IV (4.95 g.) in pyridine (15 ml.) was added to a cooled mixture of chromium trioxide (3 g.) in pyridine (50 ml.), and the whole kept (6 hr.) at room temperature with stirring. Dilution with ethyl acetate to 1.25 l., filtration through Celite, and passage over neutral alumina (40 g.) gave a clear solution from which was obtained (by evaporation) the ketone (V) (3.4 g.), m.p. 217–218°. Subsequent recrystallization from acetone afforded prisms, m.p. 233–234°, $[\alpha]_D$ −58° (in pyridine), ν_{max}^{KBr} 3340 and 1709 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{31}ClO_3$: C, 67.68; H, 8.80; Cl, 9.99. Found: C, 67.44; H, 8.62; Cl, 10.32.

6α-Chloro-17α,17β-dimethyl-18-norandrosta-4,13-dien-3-one (VI).—6β-Chloro-5α,17β-dihydroxy-17α-methylandrostan-3-one (2.75 g.) in acetic acid (275 ml.) and 36% hydrochloric acid (15 ml.) was kept with stirring at room temperature (17 hr.), and the whole then poured into ice-water and extracted with methylene dichloride. The latter solution was washed successively with water, bicarbonate solution, and again with water, dried and evaporated. Chromatography of the residue over alumina led to a crystalline solid (850 mg.) m.p. 112–114°, which was recrystallized repeatedly from ether–hexane to furnish prisms of VI (600 mg.), m.p. 117–118°, $[\alpha]_D$ −62°, λ_{max} 234 mμ, log ε 4.22; ν_{max}^{KBr} 1687, 1622, 815 and 878 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}ClO$: C, 75.32; H, 8.54; O, 5.02; Cl, 11.12. Found: C, 75.08; H, 8.54; O, 5.59; Cl, 11.57.

(18) The results of these and several hundred other steroid n.m.r. spectra will appear elsewhere (A. D. Cross and P. W. Landis, forthcoming publications).

(19) The principle of additivity of frequency shifts of the angular methyl protons due to shielding by functional groups, is well established: *cf.* (a) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); (b) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); (c) footnote 17.

(20) From our work on steroid olefins[18] and from examination of Dreiding models it is apparent that the Δ¹³-double bond in VI makes a negligible contribution to the deshielding of the 19-protons, owing to the stereochemical relation of these two groups.

(21) This figure is an average value for numerous steroidal Δ⁴-3-ketones bearing no other substituents able to shield or deshield the 19-protons.[18]

(22) We wish to thank Dr. Ralph I. Dorfman of the Worcester Foundation, Shrewsbury, Mass., for the bioassays.

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

(24) Melting points are uncorrected and were determined on the Fisher–Johns block. Rotations are for chloroform solutions, and ultraviolet spectra were taken in 95% ethanol except where stated otherwise. Infrared spectra are by Dr. J. Matthews and his staff; analyses are by Midwest Microlaboratories, Indianapolis 20, Ind., or by Dr. Bernhardt, Mülheim (Ruhr), Germany.