

of molecular models indicates that in the primary and secondary amines Va-c, the N-H bond is in fact favorably located to enter into hydrogen bonding with the C-3 ketone. To obtain evidence for the presence of such bonding, the n.m.r. spectra of Vb and Vc were examined in deuteriochloroform; attempts to similarly record the spectrum of Va failed due to its insolubility in this solvent.

In Vb and Vc the N-H proton signals were located at 10.21 and 10.86 p.p.m. downfield from tetramethylsilane. Such extreme downfield shifts clearly indicate that both compounds contain N-H protons involved in hydrogen bonds.²¹ In the case of Vb, the single olefinic proton showed a doublet pattern at 6.59 p.p.m. whereas the N-H proton exhibited a quintet at 10.21 p.p.m.²²

In spite of this evidence for hydrogen bonding, it does not appear that this bonding provides a complete answer to the observed rotational shifts. If it did then it could be reasonably expected that removal of the hydrogen bonding in Ib, $[\alpha]_D +38^\circ$ would result in a shift to a large negative rotation. On the contrary when Ib is converted either to its methyl ether derivative Vh²³ or to the *p*-chlorothiophenol derivative Vi low positive rotations, $[\alpha]_D +48.7^\circ$ and $+62^\circ$, respectively, still are observed.

Further examination of molecular models also indicate that in Va-c the R function in RNHCH= is capable of assuming almost any conformation from one approximately in the plane of the steroid ring system to one perpendicular to that plane. Similar conformations also may be achieved by the methyl ether Vh and the *p*-chlorothiophenol derivative Vi. On the other hand when tertiary amines are present, as in Vd-g, severe steric interactions exist between the methyl hydrogens (as in Ve) or the α -methylene hydrogens (as in Vd, f, g) and the C-3 ketone. In these cases, the steric effects will not permit the previously mentioned planar conformation. Rather the R groups in R₂NCH= will be forced toward conformations roughly perpendicular to the steroid plane.

The possibility that the rotatory changes may be due to these extreme conformations with their attendant effects must be considered.

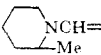
Several examples have also been collected in Tables II and III to demonstrate this effect in the 17-desmethyl and Δ^4 -3-ketone series. In the latter case while the primary and secondary amine examples already possess negative rotations very strong negative shifts are still observed in the tertiary amines.

Biological Data.—The androgenic and myotrophic activities of the compounds presented in Table IV were determined in the immature, 21-day old castrate male rat.²⁴ For oral administration the compounds were given in 0.5% tragacanth. For subcutaneous administration, the material was suspended in CMC

TABLE II
2-SUBSTITUTED-5 α -ANDROSTANE-17 β -OL-3-ONE

Substituent	Specific rotation, $[\alpha]_D^\circ$
Ia HOCH=	+60 ¹⁵
VIa H ₂ NCH=, 17-OAc	+27
VIc (C ₂ H ₅) ₂ NCH ₂ CH ₂ NHCH=, 17-OAc	+44
VIb C ₃ H ₁₀ NCH=	-256

TABLE III
2-SUBSTITUTED-17 α -METHYLANDROST-4-EN-17 β -OL-3-ONE

Substituent	Specific rotation, $[\alpha]_D^\circ$
HOCH=	+6 ¹²
H ₂ NCH=	-77.3 ²⁰
(C ₂ H ₅) ₂ NCH ₂ CH ₂ NHCH=	-101.5 ²⁰
(CH ₃) ₂ NCH=	-396.9 ²⁰
	-322.9 ²⁰

solution [aqueous solution of sodium chloride (0.5%), polysorbate 80 (0.4%), carboxymethylcellulose (0.5%), and benzyl alcohol (0.5%)].

TABLE IV
ANDROGENIC AND ANABOLIC PROPERTIES

Compound	Subcutaneous (testosterone = 100)		Oral (methyl-testosterone = 100)	
	Androgenic	Anabolic	Androgenic	Anabolic
Ib	82	230	45	320 ²⁵
IVa	10	30	40	200
IVb	<25	<25
IVc	10	<10
IVd	10	<10
Va	20	160
Vb	30	150
Vc	40	65	40	100
Vd	30	60	<50	<50
Ve	<10	<10	20	100
Vf	20	120

The androgenic activity was calculated from the weight increase of the seminal vesicles and ventral prostate and is expressed as the mean value of the two. The increase in the weight of the levator ani muscle has been used as the indication of anabolic activity. Each value represents at least two different four point assays, using five animals per dose. The activity was estimated graphically and the precision of the estimate is judged to be $\pm 50\%$.

Experimental²⁶

17 β -Hydroxy-17 α -methyl-5 α -androstane-2-phenyl[3,2-d]-pyrimidine (II).—To 10 g. of Ib in 500 ml. of ethanol was added 9.4 g. of benzamidine hydrochloride²⁷ and 40 ml. of 8% ethanolic potassium hydroxide. After 2 hr. on a steam bath, the solvent was allowed to evaporate and the residue was diluted with 250

(21) See G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **84**, 2691 (1962).

(22) While these splitting patterns are normal for the structure of Vb, the spectrum of Vc seems anomalous. Here the olefinic proton appears as a singlet at 8.95 p.p.m. and the N-H proton as a triplet at 10.86 p.p.m. At present we cannot account for the difference in the two splitting patterns nor can we account for the seemingly high displacement of the olefinic proton peak in Vc.

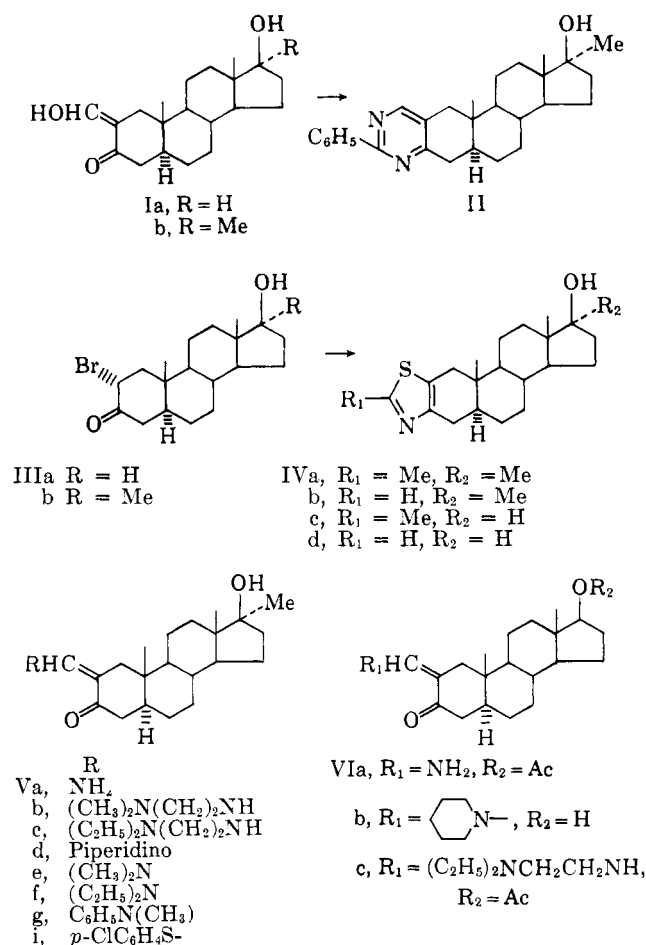
(23) J. C. Orr, O. Halpern, and A. Bowers, *J. Med. Pharm. Chem.*, **5**, 409 (1962).

(24) R. I. Dorfman, "Methods in Hormone Research," Vol. II, Academic Press, New York, N. Y., 1962.

(25) R. I. Dorfman, F. A. Kincl and H. J. Ringold, *Endocrinology*, in press.

(26) With the exception of Compounds IVa and IVb, all melting points are uncorrected and were determined on a Fisher-Johns apparatus. All rotations have been determined in chloroform unless otherwise noted. We wish to express our appreciation to Dr. J. Matthews and his staff for the recording of all infrared and ultraviolet spectra and rotations. The nuclear magnetic resonance spectra were examined in a Varian A-60 spectrometer using deuteriochloroform solution with tetramethylsilane as an internal standard.

(27) A. W. Dox, *Org. Syn., Coll. Vol. 1*, 5 (1941).



ml. of water. The solids were filtered and recrystallized from ethyl acetate-methanol to provide 2.4 g. of crystals, m.p. 241–243°. Further purification from the same solvent pair gave the analytical sample, m.p. 244–246°, $[\alpha]_D^{25} +21^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 258 m μ , $\log \epsilon$ 4.43, $\lambda_{\text{max}}^{\text{KBr}}$ 3.00 μ , 6.35 μ (m) and 6.46 μ (ms).

Anal. Calcd. for C₂₆H₃₆N₂O: C, 80.72; H, 8.71; N, 6.73; O, 3.84. Found: C, 80.69; H, 8.64; N, 6.65; O, 4.00.

2 α -Bromo-5 α -androstane-17 β -ol-3-one (IIIa).—To 13 ml. of methanol containing 1.0 g. of Ia and 400 mg. of potassium acetate was added dropwise over a period of 1 hr. 2.5 ml. of carbon tetrachloride containing 0.50 g. of bromine. The reaction mixture was maintained at 0° during the addition. A methanolic sodium methoxide (4 ml.) was then added and the mixture was heated at reflux temperature for 10 min. After dilution with water (100 ml.) the mixture was extracted with ethyl acetate (3 \times 25 ml.). The combined extracts then were washed with water, dried over sodium sulfate and evaporated to leave a gummy residue. This was chromatographed on 20 g. of neutral alumina whence elution with benzene-hexane (1:1) provided 300 mg. of crystals, m.p. 160–165°. Several crystallizations from acetone-hexane provided the pure sample, m.p. 175–177°, $[\alpha]_D^{25} +51^\circ$.²⁸

Anal. Calcd. for C₁₉H₂₉BrO₂: C, 61.78; H, 7.91; Br, 21.63; O, 8.66. Found: C, 61.99; H, 7.71; Br, 21.47; O, 8.95.

2 α -Bromo-17 α -methyl-5 α -androstane-17 β -ol-3-one (IIIb).—By a procedure identical with that described for the preparation of IIIa, 23.0 g. of Ib gave after crystallizations from acetone-hexane 16.4 g. of IIIb, m.p. 196–198°, $[\alpha]_D^{25} +19^\circ$.²⁹

Anal. Calcd. for C₂₆H₃₁BrO₂: C, 62.66; H, 8.15; Br, 20.84. Found: C, 62.43; H, 7.93; Br, 21.20.

Preparation of 2-Methylthiazoles.—A solution of ethanol (800 ml.), 2 α -bromosteroid (20 g.) and thioacetamide (20 g.) was

heated at reflux temperature for 3 hr. The mixture then was evaporated to dryness, diluted with water (1 l.) and extracted with ethyl acetate (5 \times 200 ml.). The combined extracts were washed with water, dried over sodium sulfate and evaporated. The residue was purified by chromatography or direct crystallization; a number of thiazoles were prepared.

17 β -Hydroxy-17 α -Methyl-5 α -androstane-2'-methyl[3,2-d]-thiazole (IVa) prepared from IIIb and recrystallized from acetone-hexane, m.p. 210–212°, $[\alpha]_D^{25} +47^\circ$, $[\alpha]_D^{42} +42^\circ$, $[\alpha]_D^{44} +44^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 254 m μ , $\log \epsilon$ 3.76 $\lambda_{\text{max}}^{\text{KBr}}$ 3.07 μ (ms), 6.39 μ (w); lit.⁶ m.p. 198–199.5°, $[\alpha]_D^{25} +35.6^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 254 m μ , $\log \epsilon$ 3.72.

Anal. Calcd. for C₂₂H₃₃NOS: C, 73.49; H, 9.25; N, 3.90; O, 4.45; S, 8.90. Found: C, 73.48; H, 9.22; N, 3.60; O, 4.73; S, 8.86.

17 β -Hydroxy-5 α -androstane-2'-methyl-(3,2-d)thiazole (IVc).—From IIIa: recrystallized from methylene chloride-hexane, m.p. 230–232°, $[\alpha]_D^{25} +64^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 254 m μ , $\log \epsilon$ 3.74, $\lambda_{\text{max}}^{\text{KBr}}$ 3.06 μ and 6.40 μ (ms).

Anal. Calcd. for C₂₁H₃₁NOS: C, 72.99; H, 9.04; N, 4.05; O, 4.63; S, 9.28. Found: C, 73.05; H, 9.07; N, 4.11; O, 4.43; S, 9.37.

Unsubstituted Thiazoles.—The general procedure reported above was employed with the exception that an ethereal solution of thioformamide³⁰ (30 ml.) was used for 500 mg. of 2 α -bromo steroid.

17 β -Hydroxy-17 α -methyl-5 α -androstane(3,2-d)thiazole (IVb).—Prepared from IIIb and recrystallized from acetone-hexane, m.p. 192–193°, $[\alpha]_D^{25} +33^\circ$, $[\alpha]_D^{37} +37^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 252 m μ , $\log \epsilon$ 3.61, $\lambda_{\text{max}}^{\text{KBr}}$ 3.01 μ and 6.47 μ (very-short); lit.⁶ m.p. 177–179°, $[\alpha]_D^{25} +48.8^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 251 m μ , $\log \epsilon$ 3.64.

Anal. Calcd. for C₂₁H₃₁NOS: C, 73.00; H, 9.04; S, 9.27. Found: C, 73.15; H, 8.78; S, 9.24.

17 β -Hydroxy-5 α -androstane[3,2-d]thiazole (IVd).—Prepared from IIIa and recrystallized from acetone, m.p. 245–246°, $[\alpha]_D^{25} +91^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 252 m μ , $\log \epsilon$ 3.69.

Anal. Calcd. for C₂₀H₂₉NOS: C, 72.46; H, 8.81; N, 4.22; S, 9.67. Found: C, 72.51; H, 9.06; N, 4.23; S, 9.73.

2-(Aminomethylene)-17 α -methyl-5 α -androstane-17 β -ol-3-one (Va).—Ten grams of Ib in 250 ml. of dioxane was saturated with a rapid current of dry ammonia gas during a period of 1 hr. After 2 days at room temperature, the reaction mixture was filtered to give 2.0 g. of crystals, m.p. 283–286°. Four crystallizations from methanol gave the analytical sample, m.p. 288–290°, $[\alpha]_D^{25} +35^\circ$ (pyridine), $\lambda_{\text{max}}^{\text{EtOH}}$ 316 m μ , $\log \epsilon$ 4.20, $\lambda_{\text{max}}^{\text{KBr}}$ 3.06 μ , 3.17 μ (sh), 6.07 and 6.75 μ .

Anal. Calcd. for C₂₁H₃₃NO₂: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.84; H, 10.36; N, 4.27.

2-(Aminomethylene)-5 α -androstane-17 β -ol-3-one 17-Acetate (VIa).—By the procedure described for Va, 1.0 g. of 2-hydroxy-methylene-5 α -androstane-17 β -ol-3-one 17-acetate¹⁹ gave 100 mg. of VIa, purified by recrystallization from acetone-water, m.p. 209–210°, $[\alpha]_D^{25} +27^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 314–316 m μ , $\log \epsilon$ 4.17.

Anal. Calcd. for C₂₂H₃₃NO₃·H₂O: C, 69.99; H, 9.34; N, 3.71. Found: C, 69.56; H, 9.17; N, 3.85.

2-[2'-(N,N-dimethylamino)ethylaminomethylene]-17 α -methyl-5 α -androstane-17 β -ol-3-one (Vb).—Dry benzene (1 l.) containing 50 g. of Ib and 120 ml. of N,N-dimethylethylenediamine was heated at reflux temperature for 48 hr. using a Dean-Stark water separator. The solvent then was removed by distillation at reduced pressure and the residue was diluted with water. After extraction with ethyl acetate (3 \times 200 ml.), the combined extracts were washed with water until neutral, dried over sodium sulfate, and evaporated to leave a crystalline mass which was triturated with ether. By these means, there was obtained 44.6 g. of crystals, m.p. 165–166°, which upon recrystallization from acetone gave 35.3 g. of compound, m.p. 169–171°. Further crystallization from the same solvent gave the analytical sample, m.p. 170–171°, $[\alpha]_D^{25} +61^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 328 m μ , $\log \epsilon$ 4.28, $\lambda_{\text{max}}^{\text{KBr}}$ 2.93 μ , 3.05 μ , 6.08 μ , and 6.39 μ .

Anal. Calcd. for C₂₆H₄₂N₂O₂: C, 74.58; H, 10.52; O, 7.95. Found: C, 74.24; H, 10.35; O, 8.44.

2-[2'-(N,N-diethylamino)ethylaminomethylene]-17 α -methyl-5 α -androstane-17 β -ol-3-one (Vc).—A solution of N,N-diethylethylenediamine (90 ml.) and 20 g. of Ib was stirred at room temperature for 20 hr. and then poured into 1 l. of water. After

(28) A. Butenandt, U. S. Patent 2,311,638, *Chem. Abstr.*, **37**, 4408 (1943), reports the preparation of IIIa by direct bromination of dihydrotestosterone in the presence of hydrogen bromide, m.p. 180–181°.

(29) Doorenbos and Dorn report⁶ m.p. 185–187° whereas R. E. Counsell, P. D. Klimstra and F. B. Colton, *J. Org. Chem.*, **27**, 248 (1962), report m.p. 203–206° dec., $[\alpha]_D^{25} +20^\circ$.

(30) S. Gabriel, *Ber.*, **49**, 1110 (1916).

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°, $[\alpha]_D^{20} +20^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 338–340 m μ , $\log \epsilon$ 4.18, $\lambda_{\text{max}}^{\text{KBr}}$ 3.02, 6.17 and 6.51 μ .

Anal. Calcd. for $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_2$: C, 75.30; H, 10.77; N, 6.51. Found: C, 75.06; H, 10.80; N, 6.33.

2-(2'-N,N-Diethylaminoethylaminomethylene)-5 α -androsterane-17 β -ol-3-one 17-Acetate (VIc).—By treatment of 2-hydroxymethylene-5 α -androsterane-17 β -ol-3-one 17-acetate¹⁹ as described for the preparation of Vc, there was obtained pure VIc after recrystallization from hexane, m.p. 122–123°, $[\alpha]_D^{20} +44^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 328–330 m μ , $\log \epsilon$ 4.33.

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{N}_2\text{O}_3$: 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)-17 α -methyl-5 α -androsterane-17 β -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°, $[\alpha]_D^{20} -255^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 334 m μ , $\log \epsilon$ 4.37, $\lambda_{\text{max}}^{\text{KBr}}$ 3.08, 6.15 and 6.65 μ ; lit.¹⁹ m.p. 232–239°, $[\alpha]_D^{20} -266.8^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 333 m μ , ϵ 21,100.

Anal. Calcd. for $\text{C}_{28}\text{H}_{41}\text{NO}_2$: 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)-5 α -androsterane-17 β -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°, $[\alpha]_D^{20} -256^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 334–336 m μ , $\log \epsilon$ 4.31.

Anal. Calcd. for $\text{C}_{25}\text{H}_{39}\text{NO}_2$: 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)-17 α -methyl-5 α -androsterane-17 β -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°, $[\alpha]_D^{20} -259^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 334 m μ , $\log \epsilon$ 4.25, $\lambda_{\text{max}}^{\text{KBr}}$ 2.92 μ , 6.08 μ , and 6.48 μ .

Anal. Calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_2$: 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)-17 α -methyl-5 α -andro-

sterane-17 β -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°, $[\alpha]_D^{20} -191^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 334–336 m μ , $\log \epsilon$ 4.30, $\lambda_{\text{max}}^{\text{KBr}}$ 3.01, 6.16 and 6.60 μ .

Anal. Calcd. for $\text{C}_{25}\text{H}_{41}\text{NO}_2$: 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)-17 α -methyl-5 α -androsterane-17 β -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°, $[\alpha]_D^{20} -417^\circ$ (pyridine), $\lambda_{\text{max}}^{\text{EtOH}}$ 238 and 346–348 m μ , $\log \epsilon$ 3.64 and 4.30, $\lambda_{\text{max}}^{\text{KBr}}$ 2.94, 6.06 and 6.49 μ .

Anal. Calcd. for $\text{C}_{28}\text{H}_{39}\text{NO}_2$: C, 79.76; H, 9.32; N, 3.32; O, 7.99. Found: C, 79.43; H, 9.14; N, 3.64; O, 7.99.

2-(p-Chlorophenylthiomethylene)-17 α -methyl-androsterane-17 β -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°, $[\alpha]_D^{20} +62^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 258 and 323 m μ , $\log \epsilon$ 3.60 and 4.07, $\lambda_{\text{max}}^{\text{KBr}}$ 2.92, 6.02 and 6.52 μ .

Anal. Calcd. for $\text{C}_{27}\text{H}_{35}\text{ClO}_2\text{S}$: 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 6 α - and 6 β -chlorotestosterone acetate are described. Attempts to prepare 6 α -chloro-17 α -methyltestosterone resulted in a Wagner-Meerwein rearrangement. Nuclear magnetic resonance spectral studies support the structural assignments. 6 α -Chlorotestosterone shows a favorable separation of anabolic and androgenic activities.

Although the preparations of 6-fluoro-² and 6-bromotestosterones³ have been reported, the synthesis of the 6-chloro analogs has so far not been described.^{4,5}

(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 6 β -chlorotestosterone prepared in the Syntex laboratories.

Syntheses of testosterone bearing a 6 α - and 6 β -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

(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.