Steroids. CLXXXIII.[1] New Anabolic Agents from Steroids[2]

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Condensation of 2-hydroxymethylene-17α-methyldihydrotestosterone with benzamidine hydrochloride gives a ring A fused pyrimidine. Treatment of the same starting material with a variety of amines has led to the preparation of a number of 2-aminomethylene type compounds. Certain rotational characteristics associated with these compounds are noted. Treatment of 2α-bromo-3-ketoandrostanes with either thioformamide or thioacetamide leads to the corresponding ring A fused thiazoles. The biological activity in anabolic/androgen assays of the above compounds is reported.

Recently a number of papers have appeared concerned with the preparation of steroidally fused pyrazoles,[4] isoxazoles,[2,5] and thiazoles.[2,6] In addition to these examples which are involved with fusions to the A-ring, heterocycle fusions at $C_{11}:C_{12}$,[7] $C_{16}:C_{17}$[8] and $C_{20}:C_{21}$[9] have been reported. The present paper reports a partial description of our work in this area.[10]

The condensations of β-diketones and related compounds with amidines to provide pyrimidines are well known reactions.[11] In the present case, the enol of such a system, namely, 2-hydroxymethylene-17α-methyldihydrotestosterone (Ib),[12] was allowed to react with benzamidine hydrochloride in the presence of ethanolic potassium hydroxide. By these means, moderate yields of 17β-hydroxy-17α-methyl-5α-androstane-2′-phenyl[2,3-e]pyrimidine (II) could be obtained. Oddly, repeated attempts to prepare the corresponding 2′-methyl derivative by a similar reaction with acetamidine failed.[13]

To prepare the thiazole analogs, the standard procedure[14] employing reaction of α-bromo ketones with thioacetamide or thioformamide was employed. Thus the 2-hydroxymethylene steroids Ia[15] or Ib[12] were first converted to their 2α-bromo derivatives IIIa and b by the sequence of bromination and mild alkaline hydrolysis.[16] In general, the yields of thiazoles obtained by reaction of these bromo compounds with the thioamides ranged from 20 to 40%.[17]

In addition to the above compounds, a number of substituted and unsubstituted 2-(aminomethylene)-androstanes were prepared for the purpose of evaluating their biological properties. Compounds of this class were synthesized readily by treatment of the 2-hydroxymethylene steroids Ia[15] or Ib[12] with the appropriate amine. The reaction conditions required varied according to the amine used. Recently several other laboratories[18-20] also have reported the preparation of certain 2-aminomethylene derivatives. The investigators in one of the latter groups[20] have called attention to large rotational changes which they ascribed to the replacement of the 2-hydroxymethylene group by the 2-$R_2NCH=$ function.

Examination of the rotational data in Table I indicates that the large shifts noted by Clinton, *et al.*, are not due solely to the above replacement reaction. Rather it may be seen that the sign and magnitude of the rotation of a 2-(aminomethylene)-3-keto-5α-steroid depends on the nature of the R substituents in the 2-$R_2NCH=$ function. In those cases where primary (Va) or secondary amines (Vb, c) are present, low positive rotations were observed. On the other hand when the amine is tertiary as in Vd–g, large negative rotations are found.

TABLE I

2-SUBSTITUTED 17α-METHYL-5α-ANDROSTANE 17β-OL-3-ONE

	Substituent	Specific rotations, $[\alpha]_D°$
Ib	HOCH=	+38[12]
Va	$H_2NCH=$	+35 (pyridine)
Vb	$(CH_3)_2NCH_2CH_2NHCH=$	+61
Vc	$(C_2H_5)_2NCH_2CH_2NHCH=$	+20
Vd	$C_5H_{10}NCH=$	−255
Ve	$(CH_3)_2NCH=$	−259
Vf	$(C_2H_5)_2NCH=$	−190
Vg	$C_6H_5N(CH_3)CH=$	−399
Vh	$CH_3OCH=$	+48.7[21]
Vi	p-$ClC_6H_4SCH=$	+62

At first these results seem to suggest that the magnitude of the rotation could be dependent upon the formation of hydrogen bonds between the primary and secondary amines and their C-3 ketones. Inspection

(1) Paper CLXXXII. F. A. Kincl, *Endokrinologie*, **42**, 51 (1962).

(2) For a preliminary communication see J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. Chávez Limón, L. Magaña, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).

(3) (a) Syntex Institute for Molecular Biology, 3221 Porter Drive, Palo Alto, California; (b) Worcester Foundation for Experimental Biology and Medicine, Shrewsbury, Massachusetts.

(4) R. O. Clinton, A. J. Manson, F. W. Stoner, H. C. Newman, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson and C. Carabateos, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(5) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Newman, R. G. Christiansen, A. L. Beyler, G. O. Potts and A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(6) N. J. Doorenbos and C. P. Dorn, *J. Pharm. Sci.*, **50**, 271 (1961); see also H. Antaki and V. Petrow, *J. Chem. Soc.*, 901 (1951).

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

(8) T. Komeno, *ibid.*, **8**, 680 (1960).

(9) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223 (1961).

(10) A separate manuscript by A. Bowers, *et al.*, dealing with ixoxazoles and 2-cyano compounds will be forthcoming.

(11) G. W. Kenner and A. Todd, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1957, p. 234.

(12) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(13) Private communication from A. Bowers.

(14) R. H. Wiley, D. C. England and L. C. Behr, *Org. Reactions*, **6**, 367 (1951).

(15) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959).

(16) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hange, W. P. Schneider, P. F. Beal and J. Korman, *J. Am. Chem. Soc.*, **77**, 4438 (1955).

(17) Doorenbos and Dorn[6] have claimed that the physical constants for IVa and b are in error. Redeterminations employing a carefully calibrated thermometer have given values almost identical with those originally published.[2] For a further comparison, see the constants recorded for IIIb in the Experimental section as well as those in ref. 28.

(18) G. deStevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1614 (1961).

(19) S. H. Burnstein and H. J. Ringold, *ibid.*, **26**, 3084 (1961).

(20) R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clarke, K. F. Jennings and P. E. Shaw, *ibid.*, **27**, 1148 (1962).

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° would result in a shift to a large negative rotation. On the contray when Ib is converted either to its methyl ether derivative Vh[23] or to the *p*-chlorothiophenol derivative Vi low positive rotations, $[\alpha]D$ +48.7° and +62°, 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 R_2NCH= 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 solution [aqueous solution of sodium chloride (0.5%), polysorbate 80 (0.4%), carboxymethylcellulose (0.5%), and benzyl alcohol (0.5%)].

TABLE II

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

	Substituent	Specific rotation, $[\alpha]D°$
Ia	HOCH=	+60[25]
VIa	H_2NCH=, 17-OAc	+27
VIc	$(C_2H_5)_2NCH_2CH_2NHCH$=, 17-OAc	+44
VIb	$C_5H_{10}NCH$=	−256

TABLE III

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

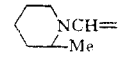
Substituent	Specific rotation, $[\alpha]D°$
HOCH=	+6[12]
H_2NCH=	−77.3[26]
$(C_2H_5)_2NCH_2CH_2NHCH$=	−101.5[26]
$(CH_3)_2NCH$=	−396.9[29]
	−322.9[30]

TABLE IV

ANDROGENIC AND ANABOLIC PROPERTIES

	Subcutaneous (testosterone = 100)		Oral (methyltestosterone = 100)	
Compound	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 ±50%.

Experimental[26]

17β-Hydroxy-17α-methyl-5α-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 hydrochloride[27] 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.

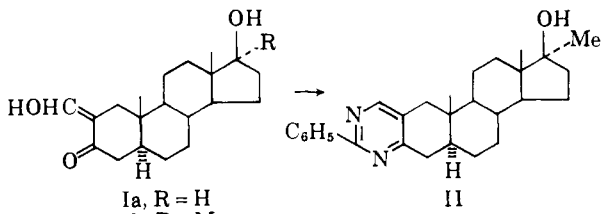
(23) J. C. Orr, O. Halpern, and A. Bowers, *J. Med. Pharm. Chem.*, **5**, 409 (1962).

(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.

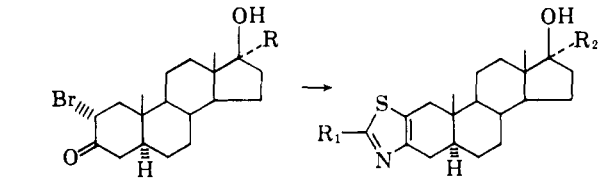
(26) With the exception of Compounds IVa and IVb, all melting points are uncorrected and were determined on a Fisher-Johns apparatus. All rotations have been determined in chloroform unless otherwise noted. We wish to express our appreciation to Dr. J. Matthews and his staff for the recording of all 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).



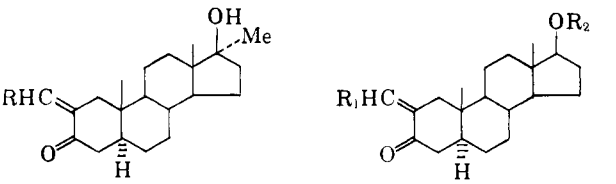
Ia, R = H
b, R = Me

II



IIIa R = H
b R = Me

IVa, R_1 = Me, R_2 = Me
b, R_1 = H, R_2 = Me
c, R_1 = Me, R_2 = H
d, R_1 = H, R_2 = H



R
Va, NH_2
b, $(CH_3)_2N(CH_2)_2NH$
c, $(C_2H_5)_2N(CH_2)_2NH$
d, Piperidino
e, $(CH_3)_2N$
f, $(C_2H_5)_2N$
g, $C_6H_5N(CH_3)$
i, p-ClC_6H_4S-

VIa, $R_1 = NH_2$, R_2 = Ac

b, R_1 =  , R_2 = H

c, $R_1 = (C_2H_5)_2NCH_2CH_2NH$, R_2 = Ac

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°, $[\alpha]D$ +21°, λ_{max}^{EtOH} 258 mμ, log ε 4.43, λ_{max}^{KBr} 3.00 μ, 6.35 μ (m) and 6.46 μ (ms).

Anal. Calcd. for $C_{28}H_{36}N_2O$: 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.

2α-Bromo-5α-androstane-17β-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. *N* 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 × 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°, $[\alpha]D$ +51°.[28]

Anal. Calcd. for $C_{19}H_{29}BrO_2$: 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.

2α-Bromo-17α-methyl-5α-androstane-17β-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°, $[\alpha]D$ +19°.[29]

Anal. Calcd. for $C_{20}H_{31}BrO_2$: 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.), 2α-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 × 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.

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

Anal. Calcd. for $C_{22}H_{33}NOS$: 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.

17β-Hydroxy-5α-androstane-2′-methyl-(3,2,-d)thiazole (IVc).—From IIIa; recrystallized from methylene chloride–hexane, m.p. 230–232°, $[\alpha]D$ +64°, λ_{max}^{EtOH} 254 mμ, log ε 3.74, λ_{max}^{KBr} 3.06 μ and 6.40 μ (ms).

Anal. Calcd. for $C_{21}H_{31}NOS$: 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 thioformamide[30] (30 ml.) was used for 500 mg. of 2α-bromo steroid.

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

Anal. Calcd. for $C_{21}H_{31}NOS$: C,73.00; H, 9.04; S, 9.27. Found: C, 73.15; H, 8.78; S, 9.24.

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

Anal. Calcd. for $C_{20}H_{29}NOS$: 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)-17α-methyl-5α-androstane-17β-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°, $[\alpha]D$ +35° (pyridine), λ_{max}^{EtOH} 316 mμ, log ε 4.20, λ_{max}^{KBr} 3.06 μ, 3.17 μ (sh), 6.07 and 6.75 μ.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.84; H, 10.36; N, 4.27.

2-(Aminomethylene)-5α-androstane-17β-ol-3-one 17-Acetate (VIa).—By the procedure described for Va, 1.0 g. of 2-hydroxymethylene-5α-androstane-17β-ol-3-one 17-acetate[19] gave 100 mg. of VIa, purified by recrystallization from acetone–water, m.p. 209–210°, $[\alpha]D$ +27°, λ_{max}^{EtOH} 314–316 mμ, log ε 4.17.

Anal. Calcd. for $C_{22}H_{33}NO_3 \cdot H_2O$: 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]-17α-methyl 5α-androstane-17β-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 × 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°, $[\alpha]D$ +61°, λ_{max}^{EtOH} 328 mμ, log ε 4.28, λ_{max}^{KBr} 2.93 μ, 3.05 μ, 6.08 μ, and 6.39 μ.

Anal. Calcd. for $C_{25}H_{42}N_2O_2$: 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]-17α-methyl-5α-androstane-17β-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 report[6] 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., $[\alpha]D$ +20°.

(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°, 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 $C_{29}H_{47}NO_2$: 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 $C_{29}H_{47}NO_2$: 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.

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

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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

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(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.