4-Sulfobutyl Thiocarbazimidate (5b).—The reaction of thiosemicarbazide (2.00 g, 22.0 mmoles) with an equimolar amount of **1b**[17] in ethanol (10 ml) gave **5b** in low yield after a relatively short (not optimal) reflux period. Crude **5b** was purified by extraction into boiling methanol and reprecipitation by the addition of ether; yield, 1.01 g (20%) as white crystals; mp 174–178°; σ^{KBr} in cm^{-1}: 3340 (m–s, sharp, NH), 1670 (m, C=N), 1160–1190 (s, broad), and 1040 (s, SO_3^-).

Anal. Calcd for $C_5H_{13}N_3O_3S_2$: C, 26.42; H, 5.76; S, 28.21. Found: C, 26.77; H, 5.72; S, 27.9.

4-(Acetimidoylthio)-1-butanesulfonic Acid.—A solution of thioacetamide (19.3 g, 25.8 mmoles) and **1b** (35.1 g, 25.8 mmoles) in benzene (100 ml) was refluxed for 2 hr and then chilled. The white crystalline precipitate was collected in two crops and triturated in boiling acetone; yield 6.90 g, mp 193–195° dec. The analytical sample, mp 196–200° dec, was recrystallized from acetic acid.

Anal. Calcd for $C_6H_{13}NO_3S_2$: C, 34.11; H, 6.20; S, 30.35. Found: C, 34.17; H, 5.99; S, 30.2.

3-(2-Thiazolin-2-ylthio)-1-propanesulfonic Acid (8a) and S-2-Aminoethyl S'-3-Sulfopropyl Dithiocarbonate (9a).—A solution of 2-thiazolidinethione (**7**) (5.00 g, 41.8 mmoles) and the sultone **1a**[15] (5.13 g, 41.8 mmoles) in 1-propanol[19] (25 ml) was refluxed for 1.5 hr and allowed to cool to room temperature. The white crystals, which had begun to deposit during the reflux period, were collected, washed with 1-propanol, acetone, and ether, and dried *in vacuo* over P_2O_5; yield of **8a**, 8.70 g (80%); mp 219–221° (melting point of analytical sample obtained from reaction in ethanol, 223–225°); σ^{KBr} in cm^{-1}: 1580 (s, C=N), 1215 (s), 1150 (s), and 1015 (s, SO_3^-).

Anal. Calcd for $C_6H_{11}NO_3S_3$: C, 29.82; H, 4.59; N, 5.80; S, 39.86. Found: C, 29.52; H, 4.88; N, 5.53; S, 40.02.

A solution of the **8a** described above in hot water (100 ml) was refluxed for 15 min and allowed to cool to room temperature. The dithiocarbonate **9a** was deposited in 2 crops (5.40 g, 50%, from **7**) as white crystals: mp 266–267°; σ^{KBr} in cm^{-1}: 1630 (s, C=O), 880 (s, SCS), 1155 (s, broad), and 1035 (s), (SO_3^-).

Anal. Calcd for $C_6H_{13}NO_4S_3$: C, 27.78; H, 5.05; N, 5.40; S, 37.08. Found: C, 28.07; H, 5.15; N, 5.32; S, 37.2.

S-2-Aminoethyl S'-4-Sulfobutyl Dithiocarbonate (9b). A solution of 2-thiazolidinethione (**7**) (15.2 g, 0.128 mole) and sultone **1b**[17] (17.4 g, 0.128 mole) in 1-propanol (125 ml) was refluxed for 3 hr and then cooled. The white crystalline precipitate (11.3 g, mp 240–245° dec), washed with ethanol and acetone, was recrystallized from water. The yield of **9b** as white crystals, mp 254–255° dec, in two crops was 4.91 g (14%); σ^{KBr} in cm^{-1}: 1640 (s, C=O), 875 (s, SCS), 1155, 1175 (broad doublet), and 1040 (SO_3^-).

Anal. Calcd for $C_7H_{15}NO_4S_4$: C, 30.75; H, 5.53; N, 5.12; S, 35.19. Found: C, 30.76; H, 5.39; N, 4.99; S, 35.1.

General Procedure for the Sulfoalkylation of Heterocyclic Thiones. Individual preparations are summarized in Table I. A solution (or suspension) of equimolar amounts of thione and sultone **1a**[15] or **1b**[17] in the appropriate solvent (ethanol or preferably 1-propanol) was refluxed for the indicated period. (Sometimes the use of a slight excess of sultone made isolation of pure products easier.) The reaction mixture was allowed to cool to room temperature; the crystalline product, which usually precipitated during the reflux period, was collected, washed thoroughly with ethanol, acetone, and ether (in that order), and dried *in vacuo* over P_2O_5. In most instances the products so obtained were analytically pure; some, however, required recrystallization.

(19) Water content by vpc: 0.5%.

Anabolic Agents. A-Ring Oxygenated Androstane Derivatives

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The synthesis of several A-ring modified dihydrotestosterone derivatives is described in detail. A comparison of the androgenic and anabolic responses produced by these A-ring isomers revealed that the C-1 oxygenated derivatives were the most potent, having a favorable separation of anabolic from the less desirable androgenic activity.

In a recent publication,[1] we reported on the interesting biological properties of various A-ring conjugated enone androstane derivatives. The most potent orally active anabolic agent of this series was found to be 17β-hydroxy-17α-methyl-5α-androst-1-en-3-one. In addition, it was found that saturation of the double bond of compound Id[1] and retention of either the carbonyl or hydroxyl function produced compounds with superior anabolic properties. These observations prompted interest in making a biological comparison (Table III) of the compounds which had a carbonyl or hydroxyl group in all of the possible positions (C-1 to C-4) of the A ring. This paper will discuss the chemistry and biology of these modifications.

The facile conversion of the 1,2α-epoxy-5α-androstan-3-one series of compounds to 1α-hydroxy-5α-androst-2-ene derivatives by treatment with hydrazine hydrate[1] afforded a convenient pathway to the 1-oxygenated A-ring androstane derivatives (III and IV) (see Table I). When the 2-dehydro-1α-hydroxy compounds (I) were reduced under catalytic conditions with platinum oxide, the corresponding saturated analogs (III) were obtained. Subsequent oxidation using chromic acid in acetone[2] afforded the 1-keto-5α-androstane derivatives (IV). An alternate pathway to the ketones IV involved oxidation of I with chromic acid in acetone[2] followed by catalytic hydrogenation of II (see Scheme I).

The synthesis of 5α-androstan-1α-ol-17-one proved to be somewhat more lengthy than that of the other 1α-hydroxy derivatives (III). This method involved protecting the 17α-hydroxy group while performing the necessary chemical changes in the A ring of the androstane molecule. The 17-tetrahydropyranyl ether of 5α-androst-2-ene-1α,17β-diol[1] was acetylated to protect the 1α-hydroxyl group. Subsequent removal of the tetrahydropyranyl group afforded a good yield of 5α-androst-2-ene-1α,17β-diol 1-acetate. Finally, treatment with chromic acid in acetone,[2] followed by base hydrolysis gave the desired 1α-hydroxy-5α-androst-2-en-17-one analog (Ia).

For the synthesis of the 2-oxygenated steroids, the reductive removal of the bromine from the appropriate

(1) P. D. Klimstra and R. E. Counsell, *J. Med. Chem.*, **8**, 98 (1965).

(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

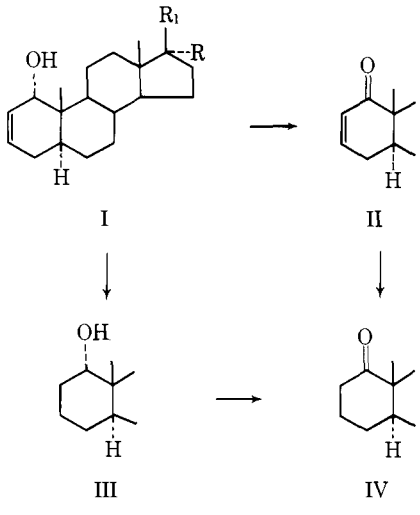
TABLE I

ISOMERIC A-RING OXYGENATED ANDROSTANE DERIVATIVES

Compd	Recrystn media	Yield, %	Mp, °C	$[\alpha]_D$, deg	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
IIIa	MeOH–H_2O	94	150–151	+101	$C_{19}H_{30}O_2$	78.57	10.41	78.68	10.41
b	MeOH–H_2O	71.4	164–165.5	+21	$C_{19}H_{32}O_2$	78.03	11.03	77.78	10.75
c	MeOH–H_2O	80	168–169	+15.5	$C_{21}H_{34}O_3$	75.40	10.25	75.28	10.15
d	Me_2CO–hexane	65	192–193	0	$C_{20}H_{34}O_2$	78.38	11.18	78.28	10.98
IVa	MeOH–H_2O	75	174–175	+204	$C_{19}H_{28}O_2$	79.12	9.79	79.30	9.94
b	MeOH–H_2O	67.4	165–167	+121.5	$C_{19}H_{30}O_2$	78.57	10.41	78.29	10.00
c	MeOH–H_2O	65	140–141	+110	$C_{21}H_{32}O_3$	75.86	9.70	75.57	9.52
d	MeOH–H_2O	93.2	173.5–175		$C_{20}H_{32}O_2$	78.89	10.59	78.72	10.33
VIa	MeOH–H_2O	46.8	188–190[a]	+102.5	$C_{19}H_{30}O_2$	78.57	10.41	78.17	10.51
b	Me_2CO–hexane	68	185–185.5		$C_{19}H_{32}O_2$	78.03	11.03	77.90	10.90
c	MeOH	35.2	170–172	+10	$C_{21}H_{34}O_3$	75.40	10.25	75.17	10.13
d	MeOH	63.4	201.5–203	+2	$C_{20}H_{34}O_2 \cdot 0.5MeOH$	76.35	11.26	76.67	11.04
VIIIa	Me_2CO–hexane	89.5	153–154[b]	+129.5	$C_{19}H_{28}O_2$	79.12	9.79	79.22	10.09
b	MeOH–H_2O	87	183–185[c]	+45.5	$C_{19}H_{30}O_2$	78.57	10.41	78.16	10.24
c	MeOH–H_2O	95.1	143–146[d]	+27	$C_{21}H_{32}O_2$	75.86	9.70	75.85	9.72
d	MeOH–H_2O	67.2	177–177.5[e]	+20	$C_{20}H_{32}O_2$	78.89	10.59	79.35	10.51
XIIIa	MeOH–H_2O	42.7	171–173	+93	$C_{19}H_{30}O_2$	78.57	10.41	78.40	10.27
b	MeOH–H_2O	69.2	179–181	+20	$C_{19}H_{32}O_2$	78.03	11.03	78.20	11.09
d	MeOH–H_2O	66.6	185–188	−2	$C_{20}H_{34}O_2$	78.38	11.18	78.45	11.02
XIVa	Acetone–H_2O	80.5	162–164	+97	$C_{19}H_{28}O_2$	79.12	9.79	79.09	9.78
b	MeOH–H_2O	35.6	150–152[f]	+25.5	$C_{19}H_{30}O_2$	78.57	10.41	78.38	10.59
c	MeOH–H_2O	50.5	140–142[g]	+7	$C_{21}H_{32}O_3$	75.86	9.70	75.99	9.70
d	MeOH–H_2O	80	169–170	−7	$C_{20}H_{32}O_2$	78.89	10.59	78.59	10.39

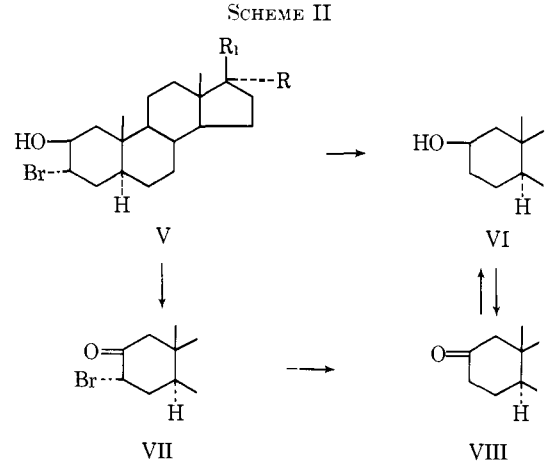
[a] Lit.[6] mp 193.5–195°, $[\alpha]^{25}D$ +101.0°. [b] C. Djerassi, R. Yaskin, and G. Rosenkranz [*J. Am. Chem. Soc.*, **72,** 5750 (1950)] reported mp 152.5–154.5°. [c] J. A. Edwards, D. G. Holton, J. C. Orr, L. C. Ibáñez, E. Necoechea, A. de la Roz, E. Segovia, R. Urguiza, and A. Bowers [*J. Med. Chem.*, **65,** 174 (1963)] reported mp 180–181°, $[\alpha]D$ +49°. [d] Lit.[6] mp 149–150°, $[\alpha]D$ +25°; R. L. Clarke, *J. Org. Chem.*, **28,** 2626 (1963). [e] Lit.[8] mp 180–181°, $[\alpha]D$ +19°. [f] Lit.[12] mp 125–126°, $[\alpha]D$ +16°. [g] P. L. Julian and H. C. Printy [U. S. Patent 2,900,399 (1959); *Chem. Abstr.*, **54,** 1622 (1960)] reported mp 175–178°.

SCHEME I



steroidal bromohydrins was investigated. Several methods have been reported for this type of transformation.[3–5] More recently, Clarke and Daum[6] described the preparation of some 2-oxygenated androstanes by treating the corresponding 3α-bromo-2β-hydroxy compounds with hydrogen using palladium chloride on strontium carbonate as catalyst. The 2-keto compounds were obtained, however, instead of the 2β-hydroxyl derivatives. These authors eventually obtained a debrominated alcohol with tributyltin hydride. In our studies, the C-2 oxygenated derivatives (VI and VIII) were obtained by a method similar to that reported by Julian and co-workers[7] in 1950. When the bromohydrins V were treated with Raney nickel in refluxing ethanol, good yields of the 2β-hydroxy compounds VI were obtained. It was found that optimal reaction periods ranged from 1–2 hr and that extended periods caused the formation of 2-keto derivatives. Subsequent treatment of VI with chromic acid in acetone[2] afforded the C-2 carbonyl derivatives VIII[3] (see Scheme II). Two alternate procedures to

SCHEME II



the 2β-hydroxy androstanes followed pathways previously described for the synthesis of 2β-hydroxy

(3) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 4224 (1954).

(4) T. Namhara and M. Yanu, *Chem. Pharm. Bull.* (Tokyo), **13,** 1004 (1965).

(5) T. Nambara and J. Fishman, *J. Org. Chem.*, **26,** 4569 (1961).

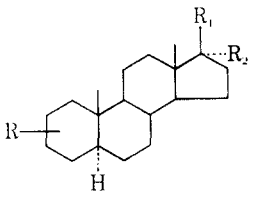
(6) R. L. Clarke and S. J. Daum, *ibid.*, **30,** 3786 (1965).

(7) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *J. Am. Chem. Soc.*, **72,** 5145 (1950).

(8) A. D. Cross, J. A. Edwards, J. C. Orr, B. Berkoz, L. Cervantes, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **6,** 162 (1963).

TABLE II

COMPARATIVE NMR DATA



Compd	R	R_1	R_2	Calcd,[a] cps C-19	Calcd,[a] cps C-18	Found, cps C-19	Found, cps C-18	X,[b] cps	Y,[c] cps	Z,[d] cps
IVa	1-one		-one	71.0	52.5	70.5	51.5			
VIIIa	2-one		-one	47.0	52.0	47.5	52.0			
IXa	3-one		-one	63.0	54.0	62.5	53.0			
XIVa	4-one		-one	46.5	52.5	46.5	52.5			
IVb	1-one	OH	H	70.0	44.5	70.0	44.5			212, 220, 227.5
VIIIb	2-one	OH	H	46.0	44.0	46.0	44.5			212, 219, 227
IXb	3-one	OH	H	62.0	46.0	62.8	46.0			212, 219.5, 228
XIVb	4-one	OH	H	45.5	44.5	46.0	44.5			210.5, 218, 225.5
IVc	1-one	OAc	H	70.0	47.5	69.5	47.5			268, 277, 285
VIIIc	2-one	OAc	H	45.0	47.0	46.0	48.0			270, 278, 286
IXc	3-one	OAc	H	62.0	49.0	61.5	48.5			268, 275, 283
XIVc	4-one	OAc	H	45.0	47.5	45.0	47.5			269, 277.5, 285
IVd	1-one	OH	CH_3	70.5	51.5	72.0	52.0			
VIIId	2-one	OH	CH_3	45.5	51.0	46.5	50.5			
IXd	3-one	OH	CH_3	62.5	53.0	62.5	53.0			
XIVd	4-one	OH	CH_3	46.0	51.5	46.5	52.0			
IIIa	1α-OH		-one	49.0	52.5	49.0	52.0	220	5.5	
VIa	2β-OH		-one	63.5	52.0	63.5	52.0	248	7.0	
Xa	3β-OH		-one	50.5	52.0	50.0	52.0	213	16.0	
XIIIa	4β-OH		-one	64.5	52.0	64.5	52.5	231	6.0	
IIIb	1α-OH	OH	H	48.5	44.5	48.0	44.0	220	6.5	210, 216.5, 223
VIb	2β-OH	OH	H	62.5	44.0	63.5	44.5	249	7.5	210, 218, 226
Xb	3β-OH	OH	H	49.0	44.0	49.0	44.0	214	20.0	[e]
XIIIb	4β-OH	OH	H	63.5	44.0	63.5	44.0	229	7.0	208, 216, 224
IIIc	1α-OH	OAc	H	48.5	47.5	47.5	47.5	221	6.0	268, 276, 283
VIc	2β-OH	OAc	H	62.5	47.0	62.5	47.5	247.5	8.0	266, 274, 282
Xc	3β-OH	OAc	H	49.5	47.0	49.0	47.0	213	17.0	267.5, 275, 284
IIId	1α-OH	OH	CH_3	49.0	51.5	49.0	51.0	222	7.0	
VId	2β-OH	OH	CH_3	63.0	51.0	63.0	51.0	248	8.0	
Xd	3β-OH	OH	CH_3	48.0	51.0	62.5	51.0	215	17.5	
XIIId	4β-OH	OH	CH_3	64.0	51.0	64.0	51.0	228	7.0	

[a] Values obtained with the use of Zürcher's tables.[14] [b] Position of proton on carbon bearing hydroxyl group in the A ring. [c] Width of band X measured at half the amplitude. [d] Position of 17α-proton observed as a triplet. [e] Peaks were masked by broad peak of 3α proton.

steroids. One of these methods[8] involved oxidation of the bromohydrins V with chromic acid in acetic acid to give the 3α-bromo 2-ketones (VII). Debromination of VII with zinc and acetic acid gave VIII. Reduction with either lithium tri-*t*-butoxyaluminum hydride (BLAH) or lithium aluminum hydride (LAH) gave a good yield of the alcohol VI. The 2β-hydroxy analogs VIb and VId were prepared by a second method involving reduction of the 2,3β-epoxide with LAH in a manner similar to the report by Slates and Wendler.[9]

Our approach to the 4-keto and 4-hydroxy steroids differed from the several methods previously employed.[10-13] A sequence of reactions similar to those described above for the preparation of the 2-keto and 2-hydroxy isomers was used to prepare some of the C-4 oxygenated androstane derivatives. Conversion of the bromohydrin XIa with Raney nickel in ethanol gave a good yield of the 4β-hydroxy derivative XIIIa. Alkylation of XIIIa with methylmagnesium bromide gave the 17α-methyl analog XIIId which was in turn oxidized with chromic acid in acetone[2] to give the C-4 carbonyl derivative XIVd (see Scheme III). An alternate pathway to compounds XIV utilized direct oxidation of the bromohydrins (XI) as described before followed by removal of the bromine with zinc and acetic acid to give the 4-keto-5α-androstanes (XIV).

In all cases, the formation of the 17β-hydroxy derivatives (IVb, VIIIb, and XIVb) necessitated starting the reaction sequence with the appropriate 17β-acetates (Ib, Vb, or XIb) and subsequently hydrolyzing with strong base to give the final product.

The nmr spectra were obtained for all of the A-ring oxygenated androstane derivatives included in this study.[14] The position of the angular methyl protons and the proton on the carbon bearing a hydroxyl group in the A ring are listed in Table II. The cal-

(9) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **78**, 3749 (1956).

(10) C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J. Chem. Soc.*, 630 (1959).

(11) K. Heusler, J. Kalvoda, P. Wieland, C. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2575 (1962).

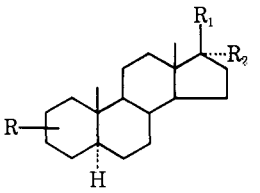
(12) K. Heusler, J. Kalvoda, C. Anner, and A. Wettstein, *ibid.*, **46**, 352 (1963).

(13) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120, 1131 (1964).

(14) We wish to thank Dr. R. H. Bible, Jr., of our laboratories for helpful discussions concerning the nmr spectra of these compounds.

TABLE III

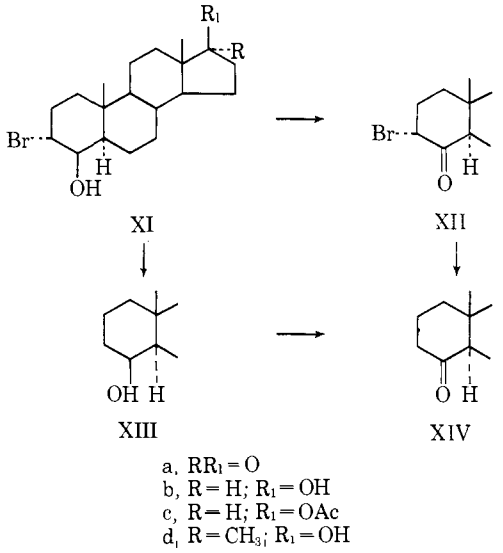
ANABOLIC–ANDROGENIC ACTIVITIES[a]



Compd	R	R_1	R_2	Im Anabolic	Im Androgenic	Oral Anabolic	Oral Androgenic
Testosterone propionate				100	100		
Testosterone				26	35		
IVb	1-one	OH	H	20	25		
VIIIb	2-one	OH	H	I	I		
IXb[b]	3-one	OH	H	100	35		
XIVb	4-one	OH	H	40	50		
IVc	1-one	OAc	H	20	10		
VIIIc	2-one	OAc	H	I	I		
IX[c]	3-one	OAc	H	20	25		
XIVc	4-one	OAc	H	10	50		
IIIb	1α-OH	OH	H	40	20		
VIb	2β-OH	OH	H	I	I		
Xb[d]	3β-OH	OH	H	4	1		
XIIIb	4β-OH	OH	H	I	I		
IIIc	1α-OH	OAc	H	20	10		
VIc	2β-OH	OAc	H	I	I		
Xc[e]	3β-OH	OAc	H	4	2.5		
Methyltestosterone				26	24	100	100
IVd	1-one	OH	CH_3	40	10	850	180
VIIId	2-one	OH	CH_3	I	I	I	I
IXd[b]	3-one	OH	CH_3	25	20	I	50
XIVd	4-one	OH	CH_3	4	1	I	I
IIId	1α-OH	OH	CH_3	25	10	650	150
VId	2β-OH	OH	CH_3	4	2.5	I	I
Xd[b]	3β-OH	OH	CH_3	2	5	I	50
XIIId	4β-OH	OH	CH_3	I	I	I	I

[a] Potencies are given in terms of per cent of the activity of testosterone propionate and 17α-methyltestosterone and were determined from the lowest levels at which significant increases in seminal vesicle or levator ani muscle weights were obtained. [b] Available from Searle Chemicals, Inc. [c] A. Ercoli and P. Ruggieri, *J. Am. Chem. Soc.*, **75**, 650 (1953). [d] L. Ruzicka, M. W. Goldberg, and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935). [e] A. Marquet, H. B. Kagan, M. Dvolaitzky, J. Lematre, and J. Jacques, *Bull. Soc. Chim. France*, 539 (1960).

SCHEME III



a, $RR_1 = O$
b, $R = H$; $R_1 = OH$
c, $R = H$; $R_1 = OAc$
d, $R = CH_3$; $R_1 = OH$

culated values for the C-19 and C-18 protons as obtained with the aid of the Zürcher tables,[15] are also included for comparative purposes.

(15) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

As shown in Table II, both the 2β-hydroxyl and 4β-hydroxyl groups (VI and XIII) produce nearly identical chemical upfield shifts of about 16–18 cps on the C-19 protons when compared to the corresponding 2- and 4-keto derivatives (VIII and XIV). This observation illustrates the spatial conformational similarity of the C-2 and C-4 positions in the normal 5α-androstane molecule.

In each case, the spatial configuration of the A-ring hydroxyl group is proven by the width of the nmr band at half the amplitude of the proton on the carbon bearing a hydroxyl group.[16] With the C-1, -2, and -4 hydroxyl derivatives (III, VI, and XIII), the protons observed have a peak width of about 5–6 cps indicating an equatorial position for the proton, whereas the C-3 hydroxyl derivatives (X) have a broad peak width of approximately 16–20 cps which is indicative of an axial proton.

Biological Results.[17,18]—The procedure used to

(16) Y. Kawazoa, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).

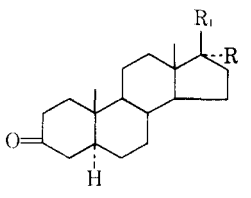
(17) We are grateful to Dr. E. F. Nutting and to Mr. R. Bergstrom of our Endocrinology Department, Division of Biological Research, for furnishing us with this information.

(18) A more detailed biological description of the isomeric A-ring oxygenated 17α-methyl-5α-androstane derivatives will be reported elsewhere: E. F. Nutting, F. Klimstra, and R. E. Counsell, submitted for publication.

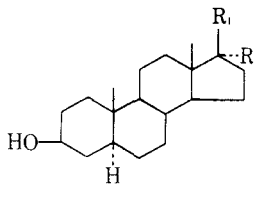
determine androgenic and anabolic activities was that of Eisenberg and Gordon[19] as modified by Saunders and Drill.[20] The compounds were given to castrated male rats by either the intramuscular or oral routes of administration. The potencies are given in terms of per cent activity of testosterone propionate (intramuscular) or 17α-methyltestosterone (oral) and were determined from the minimal levels at which significant increases in seminal vesicle and ventral prostate or levator ani muscle weights were obtained. The results listed in Table III compare the androgenic and anabolic activities for the compounds evaluated in this study.

A comparison of the parenteral potency of the various A-ring modifications of 5α-androstan-17β-ol-3-one (dihydrotestosterone) revealed that none of the isomers was as active as dihydrotestosterone. This substance possessed about the same anabolic activity as the standard, testosterone propionate, but was only one-third as androgenic. All of the other A-ring modified androstanes, whether alkylated at C-17 or not, possessed little (IIIb and IVd) or no activity when administered parenterally.

More recently, emphasis has been placed on the anabolic response observed after oral administration. One of the more common methods for effecting oral activity is by alkylation at C-17. As seen in Table III, there seem to be specific structural requirements necessary for optimal oral activity. Within the scope of the compounds studied, the C-1 position appears quite important for imparting significant oral activity. As shown in Table III, 17β-hydroxy-17α-methyl-5α-androstan-1-one (IVd) and 17β-hydroxy-17α-methyl-5α-androstan-1α-ol (IIId) were by far the most potent compounds of the entire series of A-ring isomers when administered orally, being respectively 8.5 and 6.5 times as anabolic and 1.8 and 1.5 times as androgenic as 17α-methyltestosterone. All of the other 17α-methylandrostanes studied were inactive anabolically and only the dihydromethyltestosterone isomers (IXd and Xd) had any measurable androgenic activity,



IX



X

being about 0.5 times that of methyltestosterone. It is important to emphasize that while the 3β-hydroxy and 3-keto isomers (X and IX) were considerably more androgenic than anabolic, the reverse situation resulted when the oxygen function, whether hydroxyl (III) or ketone (IV), was in the C-1 position.

During the past few years, several papers have appeared dealing with the structural requirements for biological activity of androgens at the molecular level.[21,22] Utilizing *in vivo* data, Bowers and co-workers[21] concluded that a strong factor necessary in promoting high anabolic activity was a high electron density at C-2 and/or C-3 in the 17β-hydroxyandrostane molecule. In the case of the C-3 alcohols or ketones, this requirement may be satisfied by an interconversion of the former to the latter by an *in vivo* microbiological oxidation whereupon the ketone can then enolize to present a C-2 π bond to which the receptor site can be attached. Some similar conclusions also have been reported recently by Wolff and co-workers.[22]

In the case of the compounds in our present study as well as some of those reported on previously,[23] there seems to be good indications that there are many exceptions to the above conclusions. Based on the hypotheses of Bowers and co-workers[21] and Wolff, *et al.*,[22] one would expect the greatest biological action to reside in the C-2 and/or C-3 oxygenated androstane derivatives. As shown in Table III, the C-1 oxygenated derivatives are many times more potent than the other A-ring modified androstanes. Moreover, in other studies in our laboratories, the completely saturated A-ring deoxy compound, 17α-methyl-5α-androstane,[24] possessed significant oral anabolic and androgenic activity. This compound is incapable of sp^2 hybridization in the A ring unless an oxygen function were metabolically introduced.

In conclusion, it appears that until more is known about the tissue distribution, absorption, and metabolism of these substances it is hazardous to speculate on the mode of action of these substances at the molecular-cellular level.

Experimental Section[25]

1α-Hydroxy-5α-androst-2-en-17-one (Ia). A solution of the 17-tetrahydropyranyl ether of Ib[1] (1.2 g) in pyridine (20 ml) and acetic anhydride (10 ml) was allowed to stand over the weekend at room temperature. The reaction mixture was poured into cold H_2O and extracted with ether. The extract was washed successively with 5% aqueous HCl solution, 5% aqueous $NaHCO_3$ solution, and H_2O. After drying over anhydrous Na_2SO_4 containing Darco, the solvent was removed *in vacuo* to give 1α-acetoxy-5α-androst-2-en 17β-ol 17-tetrahydropyranyl ether as an oil. The infrared spectrum indicated that the crude product was suitable for subsequent reactions.

The crude product from above (1.2 g) was allowed to stand in methanol (50 ml) containing *p*-toluenesulfonic acid monohydrate (0.7 g) at about 30° for 1.25 hr. The solution was poured into H_2O and extracted with ether. The extract was washed repeatedly with H_2O and dried (K_2CO_3) containing Darco. Solvent removal *in vacuo* left the product, 5α-androst-2-ene-1α,17β-diol 1-acetate, as an oil. Spectral determinations indicated that the crude residue was suitable for the following reaction.

A solution of crude ester (0.8 g) in acetone (15 ml) was treated dropwise with standard chromic acid solution[3] until the color of the reagent just persisted. The excess oxidizing agent was destroyed by the addition of a few drops of isopropyl alcohol. The inorganic salts were removed by filtering the solution through Supercel. The filtrate was concentrated, and the residue was diluted with H_2O. The mixture was extracted with ether and

(19) E. Eisenberg and G. S. Gordon, *J. Pharmacol. Exptl. Therap.*, **99**, 38 (1950).

(20) F. J. Saunders and V. A. Drill, *Proc. Soc. Exptl. Biol. Med.*, **94**, 646 (1957).

(21) A. Bowers, A. D. Cross, J. A. Edward, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(22) M. E. Wolff, W. Ho, and R. Kwok, *ibid.*, **7**, 577 (1964).

(23) P. D. Klimstra, E. F. Nutting, and R. E. Counsell, *ibid.*, **9**, 605 (1966).

(24) This substance was found to be 2.8 times as anabolic and 0.5 times as androgenic as methyltestosterone when given orally.[18] An initial report of activity for this substance was made earlier by C. H. Kuehakian, *Proc. Soc. Exptl. Biol. Med.*, **80**, 386 (1952).

(25) Optical rotations, spectra, and analytical data were furnished by Dr. R. T. Dillon, Mr. E. Zielinski, and Mr. J. Damascus of our Analytical department. The optical rotations and infrared spectra were obtained in chloroform at ambient temperatures. The nmr spectra were obtained with a Varian A-60 spectrophotometer and are reported in cycles per second downfield from tetramethylsilane which was used as an internal standard. Deuteriochloroform was used as the solvent unless otherwise specified. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

washed with H_2O. After drying (Na_2SO_4) the solvent was removed *in vacuo* to leave an oil. Recrystallization from acetone–hexane gave pure 1α-acetoxy-5α-androst-2-en-17-one (350 mg), mp 170–173°, $[\alpha]D$ +301.5°.

Anal. Calcd $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.99; H, 9.25.

The above acetate (0.3 g) was refluxed with methanol (8 ml) containing KOH (0.2 g) for 2 hr. The reaction was poured into H_2O and extracted with methylene chloride. The extract was washed with 5% aqueous HCl followed by 5% aqueous $NaHCO_3$ solution. After drying (Na_2SO_4) the solvent was removed *in vacuo* to give crude Ia (250 mg), mp 162–163°, $[\alpha]D$ +226°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.02; H, 9.66.

5α-Androst-2-ene-1,17-dione (IIa).—A solution of IIb[1] (0.5 g) in acetone (3 ml) was treated with standard chromic acid solution[2] dropwise until the color of the reagent persisted. The excess chromic acid was decomposed by adding a drop of isopropyl alcohol. The inorganic salts were removed by filtering through Supercel. The filtrate was concentrated *in vacuo* and diluted with H_2O. The precipitate was collected, washed with H_2O, and air dried. Recrystallization from acetone–hexane gave IIa[26] (0.35 g), mp 151–154°, λ_{max} 224.5 mμ (ε 6900).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.60; H, 9.16. Found: C, 79.67; H, 9.10.

17α-Methyl-5α-androstane-1α,17β-diol (IIId). General Method for III.—A solution of Id[1] (10 g) in ethyl alcohol (200 ml) was hydrogenated (Amico Rocker) at 70.2 kg/cm² and 100° for 20 hr using ruthenium oxide as catalyst. The catalyst was removed by filtration and the filtrate was poured into an ice-cold aqueous 2% Na_2CO_3 solution. The precipitate was collected, washed with H_2O, and air dried. Solvent removal *in vacuo* left a white solid which was recrystallized from acetone–hexane to afford IIId (6.45 g), mp 192–193°.

17α-Methyl-5α-androstan-17β-ol-1-one (IVd). General Method for IV. A. ***Via*** **Alcohol.**—A solution of IIId (1.5 g) in acetone (70 ml) was treated dropwise with standard chromic acid solution. The excess reagent was destroyed with isopropyl alcohol and the inorganic salts were removed by filtering through Supercel. The filtrate was poured into ice and H_2O and the precipitate was collected. Recrystallization from methanol–H_2O afforded IVd (1.2 g), mp 173.5–175°.

B. ***Via*** **Olefin.**—A solution of IId[1] (2.5 g) in ethyl alcohol (200 ml) was hydrogenated at atmospheric pressure and room temperature (Parr shaker) using 5% Pd–C (0.25 g) as catalyst. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residual solid was recrystallized from aqueous methanol to give IVd (2.8 g), mp 173–175°, identical with that prepared by the above procedure.

5α-Androstan-17β-ol-1-one (IVb). General Method for VIIIb and XIVb.—A solution of IVc (0.3 g) in methanol (10 ml) was refluxed with KOH (0.2 g) in water (2 ml) for 2.5 hr. The solvent was evaporated and the residual solid was taken up in a minimum of methanol and poured into H_2O. The product was collected, washed (H_2O), and air dried. Recrystallization from methanol–H_2O afforded IVb (0.175 g), mp 165–167°.

5α-Androstan-2β-ol-17-one (VIa). General Method for VI and XIII.—A mixture of Va[27] (12.0 g) in ethyl alcohol (300 ml) was refluxed with Raney nickel (45 g) for 1 hr. The solution was cooled and filtered. The filter cake was washed with ethyl alcohol and the filtrate concentrated to dryness *in vacuo* to leave a white solid. The residue was taken up in benzene and chromatographed over silica gel. Elution with benzene–ethyl acetate (4:1) gave pure VIa (5.4 g): mp 188–190°; $[\alpha]D$ 102.5°; nmr, 249 (2α-H), 63.5 (C-18 methyl), and 52 cps (C-19 methyl) [lit.[6] mp 193.5–195°; $[\alpha]^{25}D$ + 101.0°; nmr, 250 cps (2α-H)].

17α-Methyl-5α-androstane-2β,17β-diol. (VId). A. ***Via*** **Ketone.**—To a stirred solution of VIIId (1.0 g) in tetrahydrofuran (THF) (15 ml) cooled in an ice bath was added lithium tri-*t*-butoxyaluminum hydride (2.25 g) in THF (15 ml). After 1 hr at ice bath temperature, the reaction was poured into a cold 5% aqueous acetic acid solution. A finely divided precipitate was collected, washed with 5% $NaHCO_3$ solution, and dried *in vacuo*. Recrystallization from methanol afforded VId (0.85 g), mp 201.5–203°. A second crop (0.15 g), mp 191–194°, was obtained from methanol–H_2O.

B. ***Via*** **Epoxide.**—To a solution of $LiAlH_4$ (1.5 g) in purified dioxane (50 ml) was added a solution of 2,3β-epoxy-17α-methyl-5α-androstan-17β-ol[23] (3.0 g) in dioxane (50 ml) dropwise over 15 min. The reaction mixture was refluxed for 4 hr. After cooling to room temperature, the excess reagent was decomposed by the successive addition of H_2O (1.5 ml) in dioxane (20 ml), 20% aqueous NaOH (1.2 ml), and H_2O (5.2 ml). The inorganic salts were collected and washed with additional dioxane. The filtrate was concentrated *in vacuo* and the residual solid was recrystallized from methanol to give VId (2.1 g), mp 202–203°. This sample was shown by infrared spectral comparison to be identical with that obtained by the above methods.

3α-Bromo-5α-androstane-2,17-dione (VIIa).—Treatment of Va[27] with standard chromic acid solution[2] as described above gave a crude product. Recrystallization from methanol gave VIIa (4.0 g), mp 154–155°, $[\alpha]D$ +243°.

Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 62.12; H, 7.41. Found: C, 61.70; H, 7.68.

17α-Methyl-5α-androstan-17β-ol-2-one (VIIId). General Method for VIII and XIV. A. ***Via*** **Halogen.**—A mixture of VIId[1] (0.5 g) and zinc dust (0.33 g) in glacial acetic acid (6 ml) was stirred for 1 hr at room temperature. The solution was filtered to remove the zinc and poured into ice and H_2O. The product was collected, washed with H_2O, and air dried. Recrystallization from aqueous methanol afforded VIIId (0.32 g), mp 177–177.5° (lit.[8] mp 180–181°, $[\alpha]D$ + 19°).

B. ***Via*** **Alcohol.**—A solution of VId (3.5 g) in acetone (250 ml) was treated dropwise with standard chromic acid solution[2] while being cooled in a H_2O bath. The excess reagent was decomposed with isopropyl alcohol and the inorganic salts were removed through Supercel. The filtrate was concentrated to one-third of the original volume, water was added, and the solution cooled. A finely divided precipitate was collected and recrystallized from aqueous methanol to give VIIId (1.3 g), mp 173–175°. A second crop (1.0 g), mp 165–171°, was also obtained.

3α-Bromo-5α-androstane-4,17-dione (XIIa).—Treatment of XIa[28] (4.0 g) with standard chromic acid[2] as described above gave a crude product. Recrystallization from methanol gave pure XIIa (3.2 g), mp 145–146°, $[\alpha]^{25}D$ − 67.5°.

Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 62.12; H, 7.41. Found: C, 62.38; H, 7.41.

5α-Androstane-4β,17β-diol (XIIIb).—To a solution of XIIIa (0.5 g) in isopropyl alcohol (15 ml) was added a mixture of $NaBH_4$ (0.5 g) in H_2O (0.5 ml) and methanol (1.5 ml). The reaction mixture was stirred at room temperature for 5 hr and poured into ice and H_2O. After careful acidification with acetic acid, the gel-like mixture was extracted with ether. The extract was washed with H_2O and 5% $NaHCO_3$ solution and dried (Na_2SO_4 containing Darco). Solvent removal *in vacuo* left a solid which was recrystallized from aqueous methanol to give XIIIb (0.3 g), mp 179–181°.

17α-Methyl-5α-androstane-4β,17β-diol (XIIId).—A solution of XIIIa (3.0 g) in ether (100 ml) was added dropwise over 20 min to a stirred mixture of methylmagnesium bromide (50 ml, 3 *M* in ether) in ether (50 ml). The reaction was conducted in an ice bath for 0.5 hr and then refluxed for 16 hr. The mixture was decomposed by pouring into a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined extracts were washed with H_2O followed by 5% aqueous $NaHCO_3$ and dried (Na_2SO_4 containing Darco). Solvent removal *in vacuo* left a solid which was recrystallized from aqueous methanol to give XIIId (1.9 g), mp 185–188°.

17α-Methyl-5α-androstan-17β-ol-4-one (XIVd).—A stirred solution of XIIId (1.0 g) in acetone (20 ml) was treated with standard chromic acid solution dropwise until the color of the reagent persisted. The excess reagent was taken up with isopropyl alcohol. The inorganic salts were removed by filtering through Supercel. The filtrate was concentrated *in vacuo* to one-third of the original volume. Water was added, and the gelatinous material which formed was collected, washed with H_2O, and air dried to give crude XIVd, mp 150–152°. Recrystallization from aqueous methanol gave pure XIVd (0.8 g), mp 169–170°.

(26) We wish to thank Dr. A. H. Goldkamp of our laboratories for providing us with additional material on which the analytical data was obtained.

(27) P. D. Klimstra and R. E. Counsell, U. S. Patent 3,018,298 (1962); *Chem. Abstr.*, **57**, 4733 (1962).

(28) P. D. Klimstra, U. S. Patent 3,166,578 (1965); *Chem. Abstr.*, **62**, 9207 (1965).