Et_2O gave 0.33 g of **18** which was crystd from MeCN to give the anal. sample: mp 148–149°; M^+ − HOAc 334.21499. *Anal.* ($C_{22}H_{34}O_6$) C, H.

2,3-Seco-5α-*A*-norandrostane-2,3,17β-triol (19).—A soln of **18** in Et_2O was esterified with CH_2N_2. The ester (0.3 g) was dissolved in 50 ml of dry Et_2O and added to 0.7 g of LAH in 100 ml of dry Et_2O. It was refluxed and stirred for 3 hr after which no starting material remained as shown by tlc. A satd soln of Na-K tartrate was carefully added, and the mixt was filtered. The ppt was washed with Et_2O and the combined Et_2O soln was washed (dil HCl, H_2O) and evapd. The residue was crystd several times from Me_2CO giving colorless crystals: 0.05 g; mp 225–227°; M^+ 296.23624. *Anal.* ($C_{18}H_{32}O_3$) C, H.

3-Oxa-5α-androstan-17β-ol (20).—A soln of 0.040 g of **19** in PhMe contg 0.040 g of *p*-$MeC_6H_4SO_3H$ was refluxed for 3 hr and evapd under reduced pressure. The residue was dissolved in Et_2O, and the soln was washed with H_2O, dried (Na_2SO_4), and evapd to give 0.015 g of solid. Crystn from hexane gave the anal. sample, mp 121–123°, M^+ 278.22471. *Anal.* ($C_{18}H_{30}O_2$) C, H.

Heterocyclic Steroids. 3. An Androgen Having Three Heteroatoms in Ring A[1a,1b]

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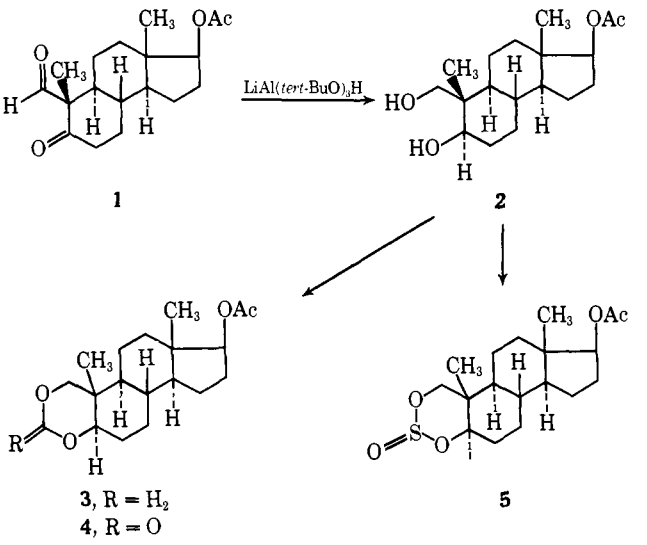
The synthesis and biological evaluation of 17β-hydroxy-2,4-dioxa-3-thia-5α-androstane 3α-oxide acetate (**5**) is described. Reduction of 17β-hydroxy-1,5-seco-*A*-trisnorandrostane-1,5-dione acetate to the corresponding 1,5-diol followed by treatment with $SOCl_2$ gave **5**. This compd had 50–100% the androgenic–myotrophic effect of testosterone. It is concluded that the activity-engendering effects of A-ring substituents are steric in nature.

In the preceding paper in this series, the activity of oxasteroids having a single heteroatom in the A ring was taken as evidence that the nature of the activity-engendering effect of groups in the A ring of steroids is steric in character. From this it was predicted that any number of heteroatoms could be inserted into the steroid nucleus to provide active compds if the steric characteristics of these atoms were appropriate to this activity. In the present work we have examined the biological consequences of replacing 3 of the 6 atoms in the A ring with heteroatoms.

Treatment of seco steroid **1**[2] with LiAl(*tert*-BuO_3)H gave diol **2**. This compd could be converted into 3 different analogs of dihydrotestosterone, one of which had 3 hetero atoms in the A ring. Thus, treatment of **2** with DMSO[3] gave the acetal **3**. When **2** was refluxed with diethyl carbonate, cyclic carbonate **4** was obtained. Lastly, when **2** was treated with $SOCl_2$, cyclic sulfite **5** was produced.



The structures of all of these substances were established and verified by nmr and mass spectra. Of special interest in this connection are the structures of acetal **3** and cyclic sulfite **5**. The 100-MHz nmr spectrum of **3** (Figure 1) shows the protons at C-1 and C-3 as 2 pairs of doublets resulting from AB splitting typical of such groups. The AB pattern from C-3 protons appears at about 4.7 and 5.1 and requires no special comment. The AB pattern from the C-1 protons, however, is of interest in connection with the corresponding pattern of the C-1 protons of cyclic sulfite **5**. In **3**, the C-1 protons form 2 doublets, one centered at approximately δ 3.3 and the other at approximately 3.85. The coupling constant of 10 Hz as well as the tilt of the peaks clearly indicates that these are protons coupled to each other. Whereas the downfield peaks are sharp, the upfield peaks are broadened. From this it is clear that the downfield peaks are due to the equatorial 1β-H, and the upfield peaks are due to the axial 1α-H. This is in harmony with the normal axial–equatorial separation of approximately 0.5 ppm for protons in cyclohexane.[4] The axial 1α-H is easily recognizable in this case because the axial 1α-H is spin-coupled to the C-19 angular Me group[5] and therefore the broadened peaks are due to this proton. Turning now to the spectrum of cyclic sulfite **5**, Figure 2, protons at C-1 again form a pair of doublets, in this case centered at approximately δ 3.6 and 4.6. However, now the broadened peak is the downfield peak at δ 4.6 and thus corresponds to the 1α-H. Therefore, the axial proton resonance has been shifted downfield by approximately 1.5 ppm from its expected position 0.5 ppm upfield from the equatorial peak. This can only be due to the deshielding of the 1α-H by the sulfone oxygen of

(1) (a) This investigation was supported in part by Public Health Service Research Grant AM 05016 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. (b) For Part 2 of this series see G. Zanati and M. E. Wolff, *J. Med. Chem.*, **14**, 958 (1971).

(2) O. R. Rodig and G. Zanati, *J. Org. Chem.*, **33**, 914 (1968).

(3) V. J. Traynelis and W. L. Hergenrother, *ibid*, **29**, 221 (1964).

(4) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden and Day, Inc., San Francisco, Calif., 1964, p 51.

(5) N. S. Bhacca and D. H. Williams, ref 4, p 118.

TABLE I

ANDROGENIC–MYOTROPHIC ASSAY

Compd (total dose, mg)	Wt, mg[a] (assay) Ventral prostate	Seminal vesicle	Levator ani	Body wt, g Initial	Final
Castrate control	19.7 ± 3.00	9.7 ± 0.43	27.7 ± 3.45	54	85
Testosterone propionate (0.6)	40.0 ± 5.05 (<0.01)	19.5 ± 0.64 (<0.001)	38.2 ± 1.15 (*ca.* 0.02)	54	90
Testosterone (3.0)	107.3 ± 7.84 (<0.001)	67.8 ± 7.18 (<0.001)	66.3 ± 2.05 (<0.001)	53	91
3 (3.0)	33.1 ± 3.39 (<0.01)	16.0 ± 0.79 (<0.05)	40.9 ± 1.61 (<0.01)	51	88
4 (3.0)	14.8 ± 1.01 (N.S.)[b]	10.2 ± 0.22 (N.S.)	22.9 ± 2.77 (N.S.)	54	87
5 (3.0)	52.4 ± 1.52 (<0.001)	38.5 ± 1.90 (<0.001)	64.3 ± 1.52 (<0.001)	54	90

[a] Mean ± standard error. [b] Not significant.

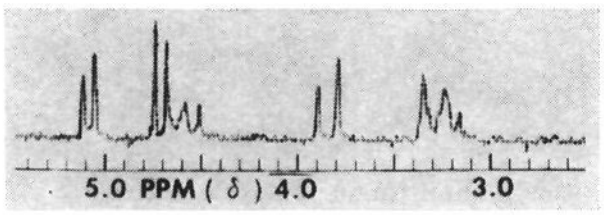


Figure 1.—Portion of 100-MHz nmr spectrum of **3**.

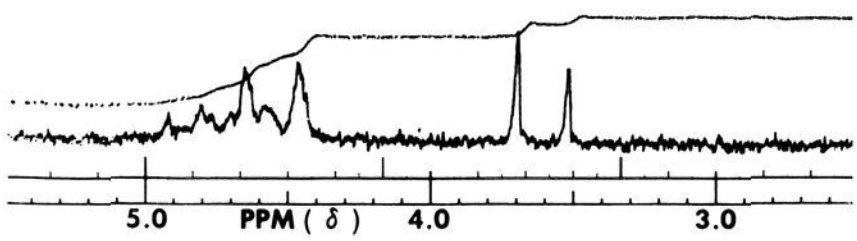


Figure 2.—Portion of 60-MHz nmr spectrum of **5**.

the cyclic sulfite and it is clear, therefore, that the sulfone oxygen is on the α side of the steroid rather than being present as the β isomer.† The preferential formation of the α isomer is probably due to a repulsive interaction in the β isomer with the 19-angular methyl group. The C-1 protons of the cyclic carbonate **4** appear as a broad singlet rather than as a pair of doublets, and this reflects the more symmetrical effect of the carbonyl group at C-3. In the case of **3**, **4**, and **5**, the 5α-H uniformly appears as a multiplet in the region of the C-1 protons.

Discussion

The data from the biological testing are displayed in Table I.[6] It can be seen that **3** and **5** are active as androgens. The lack of activity of **4** may be due to facile hydrolysis of this cyclic carbonate. Compd **5** is an androgen in which 3 of the 6 atoms in the A ring are replaced by heteroatoms. The activity of this compd, which is clearly extremely different from dihydrotestosterone in its electronic characteristics in the A ring, provides convincing support for the concept that it is neither the electronic nor hydrophobic bonding characteristics of the atoms in ring A but their steric properties which are the dominant factors in engendering biological activity in the androgen molecule.

† NOTE ADDED IN PROOF. Since this paper was written, the structure of **5** has been determined by X-ray diffraction by Dr. William L. Duax of Medical Foundation of Buffalo Research Laboratories, Buffalo, New York. The X-ray findings confirm the α-axial orientation of the sulfone oxygen atom.

(6) Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis., using essentially the method of L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175 (1953).

Experimental Section[7]

1,5-Seco-*A*-trisnorandrostane-1,5β,17β-triol 17-Acetate (2).—A soln of 0.30 g of **1**[2] in 6 ml of anhyd THF was added to a soln of 0.60 g of LiAl(*tert*-BuO)$_3$H in 12 ml of THF at 0° during 15 min and then stirred overnight at room temp. It was decompd with 60 ml of 5% HoAc, and the product was extd with Et_2O, washed with 10% $NaHCO_3$ soln and then H_2O, dried (Na_2SO_4), and evapd. The product was crystd from Me_2CO to afford a pure sample: mp 223–224°; $M^+ - H_2O$ 292. *Anal.* ($C_{18}H_{30}O_4$) C, H.

2,4-Dioxa-5α-androstan-17β-ol Acetate (3).—A soln of 0.10 g of **2** in 10 ml of DMSO was refluxed for 1 hr and cooled. H_2O was added and the reaction mixt was extd with Et_2O several times. The Et_2O was removed under vacuum and the residue was purified on a silica gel plate using hexane–Me_2CO to give 50 mg of pure product. The anal. sample had mp 120–120.5° after recrystn from hexane–Me_2CO, $M^+ - H_2CO$ 292.20468. *Anal.* ($C_{19}H_{30}O_4$) C, H.

17β-Hydroxy-2,4-dioxa-5α-androstan-3-one Acetate (4).—A mixt of 0.20 g of **2**, 0.05 g of NaOEt, and 12 ml of $CO(OEt)_2$ was refluxed for 3 hr, cooled, and dild with 100 ml of Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and evapd under reduced pressure. The residue was recrystd from hexane–Et_2O to give the anal. sample: mp 185–187°; M^+ 336.19355. *Anal.* ($C_{19}H_{28}O_5$) C, H.

17β-Hydroxy-2,4-dioxa-3-thia-5α-androstane 3α-Oxide Acetate (5).—A mixt of 0.10 g of **2**, 1 ml of C_6H_6, and 1 ml of $SOCl_2$ was kept at 25° for 3 hr and poured into ice water. The product was extd with Et_2O, and the washed, dried (Na_2SO_4) Et_2O extract was evapd to give a solid which was purified by tlc (hexane–Me_2CO) and recrystd from hexane to give the anal. sample: mp 125–125.5°; $M^+ - SO_2$ 292.19570. SO_2 was also identified in the mass spectrum; M^+ 63.96140. *Anal.* ($C_{18}H_{28}O_5S$) C, H, S.

(7) Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Nmr spectra were obtained at 60 MHz on samples in $CDCl_3$ on a Varian A-60A instrument or at 100 MHz on a Jeolco JMH-100 instrument (TMS). Mass spectra were obtained by Mr. William Garland on a MS-902 high-rsolution instrument. Where analyses are indicated only by symbols of the elements or functions, anal. results obtained for those elements or functions were within ±0.4% of the theor values.