3-Methoxyhydrocinnamonitrile (37) was prepd from 32.0 g (0.2 mole) of 36 by method B: yield, 32.1 g (100%); bp 110–120° (0.5 mm). *Anal.* ($C_{10}H_{11}NO$) C, H, N.

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# Heterocyclic Steroids. 4.[1] Synthesis and Androgenic Activity of A-Ring Homosteroids†

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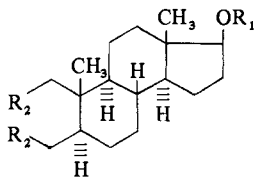
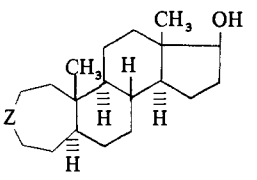
The synthesis of 3-oxa-, 3-thia-, 3-selena-, 3-tellura-*A*-homo-5α-androstan-17β-ol derivatives and 3,4-dithia-*A*-bishomo-5α-androstan-17β-ol by cyclization of appropriate seco compounds is described. All of the compounds except the tellurio derivative show both androgenic and myotrophic activity. The thia derivative is the most active; showing levator ani activity equivalent to testosterone but weaker seminal vesicle effects.

The results of our recent work on *A*-nor heterocyclic steroids[2-4] and 6-membered A-ring heterocyclic steroids[1,5] have prompted the present study in the preparation and activity of the corresponding *A*-homo compounds.

For the preparation of oxasteroid 6, diester 1[2] was reduced with LAH to give diol 2, which on refluxing in PhMe containing *p*-TsOH gave the desired 6. The other heterocyclic homosteroids were obtained by protecting the 17β-OH in 1 as the tetrahydropyranyl ether 3 and subsequent reduction with LAH to give diol 4. Formation of the dimesylate 5 and cyclization in the presence of $Na_2S$, $Na_2Se$,[6] $Na_2Te$,[7] or $Na_2S_2$[8] and cleavage of protecting groups gave the desired 7, 8, 9, and 10, respectively.





1, $R_2$ = $CO_2Me$; $R_1$ = H
2, $R_2$ = $CH_2OH$; $R_1$ = H
3, $R_2$ = $CO_2Me$; $R_1$ = $-\overline{CH(CH_2)_4O}$;
4, $R_2$ = $CH_2OH$; $R_1$ = $-\overline{CH(CH_2)_4O}$;
5, $R_2$ = $CH_2OM_S$; $R_1$ = $-\overline{CH(CH_2)_4O}$;

6, Z = O
7, Z = S
8, Z = Se
9, Z = Te
10, Z = SS

## Results and Discussion

The data from the pharmacological testing‡ are displayed in Table I.

It can be seen that the oxa-, thia-, and selena-*A*-homo steroids (6, 7, and 8) are active compounds, whereas the tellurio derivative 9 is inactive. This is in contrast to the *A*-nor series in which the oxa derivative is inactive, whereas the tellurio derivative is active. The difference between the two series is probably a result of the change in size of the rings. In the androgenic indexes, as shown by the ventral prostate and seminal vesicle weights, the most active compound is the thia compound 7, and both the oxa derivative 6 and the Se derivative 8 are less active. In myotrophic activity response, as shown by the levator ani test, the oxa compound 6 and the thia compound 7 are of similar activity with the Se compound being less active. The 8-membered A ring disulfide 10 is roughly comparable in activity to the oxa compound in all of the tests. The oxa and thia compounds 6 and 7 are equivalent in myotrophic activity to testosterone, whereas even the strongest androgen (7) is less active than testosterone in the ventral prostate test. In this connection, it is of interest that prior examinations of activity of carbo-

Table I. Androgenic–Myotrophic Assay

| Compd (total dose), mg | | Wt, mg[a] Ventral prostate | Seminal vesicle | Levator ani | Body wt, g Initial | Final |
|---|---|---|---|---|---|---|
| Castrate control | | 15.3 ± 0.23 | 10.4 ± 0.47 | 22.6 ± 3.04 | 55 | 87 |
| Testosterone (0.3) | | 33.3 ± 2.66 | 13.7 ± 1.12 | 31.7 ± 1.16 | 54 | 96 |
| *p* | | <0.001 | <0.05 | <0.05 | | |
| Testosterone (3.0) | | 90.3 ± 6.19 | 77.9 ± 1.75 | 55.2 ± 1.82 | 54 | 97 |
| *p* | | <0.001 | <0.001 | <0.001 | | |
| 6 (3.0) | O | 43.0 ± 2.40 | 23.8 ± 1.25 | 53.5 ± 1.49 | 54 | 91 |
| *p* | | <0.001 | <0.001 | <0.001 | | |
| 7 (3.0) | S | 65.8 ± 1.44 | 32.2 ± 1.09 | 53.7 ± 1.02 | 58 | 95 |
| *p* | | <0.001 | <0.001 | <0.001 | | |
| 8 (3.0) | Se | 40.05 ± 4.18 | 18.4 ± 1.43 | 42.1 ± 1.56 | 54 | 92 |
| *p* | | <0.001 | <0.001 | <0.001 | | |
| 9 (3.0) | Te | 17.8 ± 0.01 | 11.1 ± 0.31 | 17.6 ± 0.80 | 54 | 76 |
| *p* | | <0.05 | NS[b] | NS | | |
| 10 (3.0) | SS | 42.0 ± 5.92 | 23.4 ± 0.34 | 50.3 ± 1.35 | 54 | 95 |
| *p* | | <0.01 | <0.001 | <0.001 | | |

[a] Mean ± S.E. at $p = 0.001$. [b] Not significant.

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‡Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis. using essentially the method of Hershberger, *et al.*[9]

cyclic *A*-homo steroids have shown that pure samples of 17β-hydroxy-*A*-homoandrost-4a-en-3-one acetate are inactive,[10] in contrast to earlier results on impure samples,[11] and the dehydro derivative, 17β-hydroxy-*A*-homo-5α-androstan-4a-one, is also inactive.[12]

Our own work[5] has given rise to the concept that it is neither the electronic nor the 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. It is pertinent, therefore, to inquire what the conformations of ring A in the present steroids might be. There is evidence[13-15] which indicates that the stable conformation of cycloheptane is a somewhat deformed chair. Models of the present *A*-homo steroids indicate that two such deformed chairs as well as flexible twist boat forms are possible.

It is clearly not possible to decide *a priori* which of these forms is capable of interaction with a receptor. On the other hand, the differences in activity between, for example, *A*-homo, *A*-nor, and 6-membered oxasteroids appear to form a pattern. We are currently making acyclic derivatives§ which should shed some light on the reality of this pattern and from which it may be possible to derive a more complete general principle for the activity requirements in the A ring of androgens.

## Experimental Section#

**17β-Hydroxy-2,3-seco-5α-androstane-2,3,17β-triol (2).** A soln of 0.5 g of **1**[2] in 80 ml of dry $Et_2O$ was added to 0.6 g of LAH in 100 ml of dry $Et_2O$. The resulting soln was refluxed and stirred for 3 hr, treated carefully with a satd soln of Na-K tartrate, and filtered. The ppt was washed with $Et_2O$ and the combined $Et_2O$ soln was washed (dil HCl, $H_2O$), dried ($Na_2SO_4$), and evapd. The residue was crystd several times from $Me_2CO$ giving 0.39 g of colorless crystals, mp 220–222°, $M^+$ 310, $M^+ - C_2H_4OH$ 265.21648. *Anal.* ($C_{19}H_{34}O_3$) C, H.

**17β-Hydroxy-2,3-seco-5α-androstane-2,3,17β-triol 17-(2-Tetrahydropyranyl) Ether (4).** A soln of 2 g of **1**[2] in 100 ml of dry dihydropyran contg a drop of $POCl_3$ was stirred at 25° for 15 min and then evapd under reduced pressure. The residue was dissolved in $Et_2O$, washed ($NaHCO_3$ soln, $H_2O$), dried ($Na_2SO_4$), and evapd. The crude **3** was dissolved in 200 ml of dry $Et_2O$ and added to 2 g of LAH in 150 ml of $Et_2O$. The soln was refluxed and stirred for 2 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, $H_2O$), dried ($Na_2SO_4$), and evapd. The residue was crystd several times from $Me_2CO$ giving 1.3 g of colorless crystals, mp 168–170°. *Anal.* ($C_{24}H_{42}O_4$) C, H.

***A*-Homo-3-oxa-5α-androstan-17β-ol (6).** A soln of 0.13 g of **2** in PhMe contg 0.11 g of *p*-TsOH was refluxed for 2 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 0.10 g of solid. Crystn from $Et_2O$–hexane gave 0.08 g of product, mp 138–141°, $M^+$ 292.24056. *Anal.* ($C_{19}H_{32}O_2$) C, H.

***A*-Homo-3-thia-5α-androstan-17β-ol (7).** To a cold soln of 0.6 g of **4** in 10 ml of pyridine there was added dropwise, with stirring, a cold soln of 0.5 g of $MeSO_2Cl$ in 3 ml of pyridine. After the addn was complete, the reaction mixt was stirred at 25° for 3 hr, diluted with ice–$H_2O$ (200 ml), extd with $Et_2O$, washed ($NaHCO_3$ soln, $H_2O$), dried ($Na_2SO_4$), and evapd to give crude **5**. A mixt of 0.1 g of crude **5**, 80 ml of 80% EtOH, and 0.3 g of $Na_2S$ was heated under reflux for 8 hr, cooled, and diluted with $H_2O$. The mixt was extd with $Et_2O$, washed (HCl, $NaHCO_3$ soln, $H_2O$), dried ($Na_2SO_4$), and evapd to give crude tetrahydropyranyl ether. The protecting ether group was hydrolyzed at 60° in 10 ml of EtOH contg 3 drops of HCl and 1 ml of $H_2O$ during 5 min. The soln was cooled, evapd, and extd with $Et_2O$ to afford 0.045 g of solid material. Several crystns from $Et_2O$–hexane gave the analytical sample, mp 126–128°, $M^+$ 308, $M^+ - S$ 276.246477. *Anal.* ($C_{19}H_{32}OS$) C, H.

**3-Selena-*A*-homo-5α-androstan-17β-ol (8).** A soln of 0.1 g of **5** and 0.4 g of $Na_2Se$ in 100 ml of EtOH was heated at reflux for 3 hr and worked up as for **7** to afford 0.04 g of **8**, mp 131–133°, $M^+$ 356. *Anal.* ($C_{19}H_{32}OSe \cdot H_2O$) C, calcd for H, 9.12, found, 8.64.

**3-Tellura-*A*-homo-5α-androstan-17β-ol (9).** A soln of 0.1 g of **5** and 0.3 g of $Na_2Te$ in 100 ml of EtOH was heated at reflux for 2 hr and was worked up as for **7** to afford 0.055 g of **9**, mp 100–103°, $M^+$ 404. This compd decompd on standing for several weeks. *Anal.* ($C_{19}H_{32}OTe$) C, H.

**3,4-Dithia-*A*-bishomo-5α-androstan-17β-ol (10).** A soln of 0.1 g of **5** and a tenfold excess of $Na_2S_2$ in 50 ml of EtOH was heated at reflux for 3 hr and was worked up as for **7** to afford 0.06 g of **10**, mp 120–122°, $M^+$ 340. *Anal.* ($C_{19}H_{32}OS_2$) C, H, S.

§M. E. Wolff and G. Zanati, unpublished studies.

#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. Mass spectra were obtained on an AEI MS-902 instrument (70ev) by Dr. Robert Weinkam or Mr. W. Garland. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

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