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Heterocyclic Steroids. 5.[1] Sulfur, Selenium, and Tellurium 5α-Androstane Derivatives and Their 7α-Methylated Congeners†

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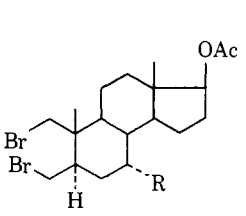
As part of a continuing program in the preparation of ring A modified androgens, the preparation of some additional sulfur, selenium, and tellurium derivatives was undertaken.

The 7α-methyl steroids **8–10** were obtained by treatment of 7α-methyl-1,4-dibromo-1,4-seco-2,3-bisnor-5α-androstan-17β-ol acetate (**2**)[2] with Na_2Se, Na_2Te, and Na_2S_2, respectively, in refluxing ethanol. This sequence was taken from our previous preparation[3] of **4–7**, and the details of the preparation of these compounds are given in the Experimental Section. The 17α-alkyl thiasteroid **11** was prepared by Oppenauer oxidation of 7α-methyl-2-thia-*A*-nor-5α-androstan-17β-ol[2] to give ketone **12** which on treatment with MeMgBr gave **11**. A similar sequence gave the 19-nor derivatives **14** and **15**.

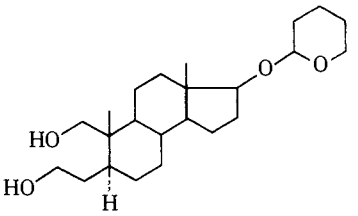
A thiasteroid containing a six-membered A ring (**13**) was produced by esterification of 17β-hydroxy-1,2-seco-*A*-nor-5α-androstane-1,3-dioic acid[4] followed by formation of the C-17 tetrahydropyranyl ether. Reduction of the last compound with $LiAlH_4$ gave **3**, which was converted to the dimesylate and then to **13** using Na_2S.

The data from the biological testing are given in Table I.‡ As described in our previous work,[2,3] the activity of the heterocyclic androstane derivatives rises in the order S ~ Se < Te < S-S, and the introduction of the 7α-methyl group enhances the activity of *A*-nor thiasteroids. By contrast, the present results show that the introduction of the 7α-methyl group into the Se, Te, and S-S derivatives does not raise activity.

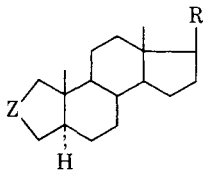
The activity of the six-membered thiasteroid **13** is most interesting. This compound would be isosteric with a seven-membered carbocyclic ring containing a Δ^2 double bond. Compound **13** has only about one-fifth the androgenic activity of testosterone, but the levator ani response is nearly as high as that of testosterone. In this respect, it is quite similar to the corresponding 2-oxa analog.[5] All of these data are in harmony with our postulate[3] of the importance of an A ring, equivalent in size to a six-membered or larger carbocyclic ring, flattened in the vicinity of C-2 and C-3, for androgenic–myotrophic activity.



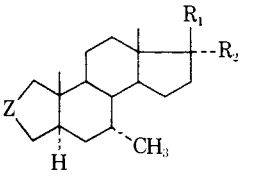
1, R = H
2, R = Me



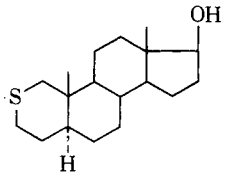
3



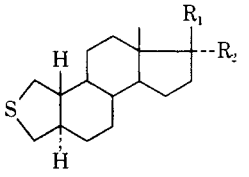
4, Z = Se; R = OH
5, Z = Se; R = OAc
6, Z = Te; R = OH
7, Z = S-S; R = OAc



8, Z = Se; R_1 = OH; R_2 = H
9, Z = Te; R_1 = OH; R_2 = H
10, Z = S-S; R_1 = OH; R_2 = H
11, Z = S; R_1 = OH; R_2 = CH_3
12, Z = S; R_2, R_3 = O



13



14, R_1R_2 = O
15, R_1 = OH; R_2 = Et

Experimental Section**

2-Selena-*A*-nor-5α-androstan-17β-ol (**4**). To a solution of 0.4 g of **1**[7] in 100 ml of refluxing EtOH there was added a tenfold excess of Na_2Se. Heating was continued for 24 hr when tlc indicated complete conversion of the dibromide to the product. The solution was poured into 600 ml of H_2O, acidified to pH 3, and extracted with Et_2O three times. The Et_2O extract was washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to give 0.25 g of **4** as a white solid. Several recrystallizations from Et_2O–hexane gave the analytical sample: mp 157–159°; M^+ 328; *m/e* 328 (M^+), 248.2142 (M^+ − Se); nmr 0.75, 0.83 ppm (C-18 and C-19). *Anal.* ($C_{17}H_{28}OSe \cdot H_2O$) C, H.

2-Selena-*A*-nor-5α-androstan-17β-ol Acetate (**5**). A solution of 0.1 g of **4** in 4 ml of pyridine and 2 ml of Ac_2O was kept overnight at 25°, poured into 100 ml of ice–H_2O, acidified with HCl, and extracted with Et_2O. The Et_2O was washed several times with H_2O, dried ($NaSO_4$), and evaporated to give an oil, which was crystallized from hexane to give the analytical sample: mp 92–94°. *Anal.* Calcd for $C_{19}H_{30}O_2Se \cdot H_2O$: C, 58.91; H, 8.26. Found: C, 58.82; H, 7.77.

2-Telluria-*A*-nor-5α-androstan-17β-ol (**6**). A refluxing solution of 0.3 g of **1** in 100 ml of refluxing EtOH containing tenfold excess of Na_2Te was allowed to react and worked up as described for **4**.

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‡Taken in part from the Ph.D. Thesis of G. Gaare, University of California, San Francisco, Calif., 1972.

§This paper is dedicated to my postdoctoral professor, Alfred Burger (1955–1957).

‡Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis., using essentially the method of Hershberger, *et al.*[6]

**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 by Mr. William Garland or Dr. Robert Weinkam on a MS-902 high-resolution instrument. 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.

Table I. Androgenic–Myotrophic Assay

Compd (total dose, mg)	Wt, mg[a]			Body wt, g	
	Ventral prostate	Seminal vesicle	Levator ani	Initial	Final
Castrate control	15.6 ± 0.41	11.8 ± 0.30	27.0 ± 1.35	55	94
Testosterone (0.3)	25.6 ± 2.47	15.1 ± 0.76	31.4 ± 2.50	55	96
Testosterone (0.6)	52.5 ± 3.48, $p < 0.001$	21.8 ± 2.35, $p < 0.01$	37.6 ± 1.89, $p < 0.01$	55	97
Testosterone (3.0)	90.3 ± 6.19, $p < 0.001$	77.9 ± 1.75, $p < 0.001$	55.2 ± 1.82, $p < 0.001$	54	97
8 (3.0)	88.1 ± 3.55, $p < 0.001$	70.0 ± 2.24, $p < 0.001$	67.3 ± 2.12, $p < 0.001$	53	97
9 (3.0)	72.8 ± 1.58, $p < 0.001$	55.4 ± 1.74, $p < 0.001$	64.1 ± 2.04, $p < 0.001$	54	92
10 (3.0)	91.6 ± 4.75, $p < 0.001$	72.6 ± 4.73, $p < 0.001$	66.1 ± 0.96, $p < 0.001$	54	90
11 (3.0)	123.5 ± 5.70, $p < 0.001$	81.6 ± 3.52, $p < 0.001$	75.1 ± 4.61, $p < 0.001$	54	97
13 (3.0)	54.2 ± 1.57, $p < 0.001$	33.6 ± 1.17, $p < 0.001$	60.2 ± 1.85, $p < 0.001$	51	89

[a] Mean ± S.E.

After crystallization from Et_2O–hexane, the analytical sample had mp 145–146°: *m/e* 378.1200 (M^+); nmr 0.78, 0.85 ppm (C-18 and C-19). *Anal.* ($C_{17}H_{28}OTe$) C, H.

2,3-Dithia-5α-androstan-17β-ol Acetate (7). A tenfold excess of Na_2S_2 dissolved in the minimum amount of EtOH and 100 mg of **1** in 30 ml of EtOH was refluxed for 7 hr, when tlc indicated complete conversion of dibromide to the desired product. The solvent was removed under vacuum and the residue was poured into acidified ice–H_2O and extracted with Et_2O. The extract was washed with dilute HCl and H_2O, dried (Na_2SO_4), and purified by tlc using hexane–acetone to give 0.05 g of the desired compound as a solid. It was crystallized from Et_2O–hexane to give the analytical sample: mp 153–154°; *m/e* 354.1688 (M^+); nmr 0.79, 1.08 ppm (C-18 and C-19). *Anal.* ($C_{19}H_{30}O_2S_2$) C, H.

7α-Methyl-2-selena-*A*-nor-5α-androstan-17β-ol (8). A refluxing solution of 0.250 g of **2**[2] in 50 ml of EtOH containing a tenfold excess of Na_2S was allowed to react and worked up as described for **4**. The solid was crystallized from Me_2CO–hexane to give 0.05 g of product: mp 142–144°. *Anal.* ($C_{18}H_{30}OSe$) C, H.

7α-Methyl-2-telluria-*A*-nor-5α-androstan-17β-ol (9). A refluxing solution of 0.250 g of **2** in 50 ml of EtOH containing a tenfold excess of Na_2Te was allowed to react and was worked up as described for **4**. The residue was crystallized from MeCO–hexane to yield 0.04 g of product: mp 154–156°. *Anal.* ($C_{18}H_{30}OTe$) C, H.

7α-Methyl-2,3-dithia-5α-androstan-17β-ol (10). A solution of 0.250 g of **2** in 50 ml of EtOH containing a tenfold excess of Na_2S_2 was allowed to react and worked up in a manner similar to that used for the preparation of **4**. The product was recrystallized from hexane to give 0.025 g of product with mp 115–117°. *Anal.* ($C_{18}H_{30}OS_2$) C, H.

7α,17α-Dimethyl-2-thia-*A*-nor-5α-androstan-17β-ol (11). A solution of 0.1 g of **12** and 3 ml of CH_3MgBr (3 *M* in Et_2O) in 20 ml of Et_2O was refluxed for 8 hr, poured into acidified ice–H_2O, and extracted with Et_2O. The ether extracts were thoroughly washed with $NaHCO_3$ solution and H_2O. After removing the solvent under vacuum, the residue was purified by recrystallization from Me_2CO–hexane to yield 0.045 g of colorless crystals: mp 174–176°. *Anal.* ($C_{19}H_{32}SO$) C, H.

7α-Methyl-2-thia-*A*-nor-5α-androstan-17-one (12). A mixture of freshly distilled toluene (25 ml), dry cyclohexanone (1.5 ml) and 0.3 g of aluminum isopropoxide, and 0.150 g of 7α-methyl-2-thia-*A*-nor-5α-androstan-17β-ol[2] was refluxed for 14 hr. At this time tlc revealed no starting material, and the reaction mixture was evaporated under vacuum, poured into acidified ice–H_2O, and extracted with Et_2O. The extracts were thoroughly washed with 5% $NaHCO_3$ solution and H_2O before being dried (Na_2SO_4) and evaporated. The oily residue was purified by preparative tlc and recrystallized from MeOH to yield 0.110 g of crystals: mp 146–148°. *Anal.* ($C_{18}H_{28}SO$) C, H.

1,2-Seco-*A*-nor-5α-androstane-1,3,17β-triol 17-(2′-Tetrahydropyranol) Ether (13). 17β-Hydroxy-1,2-seco-*A*-nor-5α-androstane-1,3-dioic acid[4] was treated with CH_2N_2 in Et_2O to give the corresponding dimethyl ester. A solution of 0.5 g of this diester in 50 ml of dry dihydropyran and a drop of $POCl_3$ was stirred at 25° for 1 hr and evaporated under reduced pressure. The residue was dissolved in Et_2O, washed ($NaHCO_3$ solution, H_2O), dried (Na_2SO_4), and evaporated to give the crude tetrahydropyranyl ether. This tetrahydropyranyl ether (0.3 g) was dissolved in 50 ml of dry Et_2O and added to 0.5 g of $LiAlH_4$ in 100 ml of dry Et_2O. It was refluxed and stirred for 3 hr. A saturated solution of sodium potassium tartrate was carefully added and the mixture was filtered. The precipitate was washed with Et_2O and the Et_2O solution was washed (dilute HCl, H_2O), dried (Na_2SO_4), and evaporated. The residue was crystallized from Me_2CO giving colorless crystals: mp 155–158°. *Anal.* ($C_{23}H_{40}O_4$) C, H.

2-Thia-5α-androstan-17β-ol (13). To a cold solution of 0.15 g of **3** in 3 ml of pyridine was added dropwise, with stirring, a cold solution of 0.15 g of $MeSO_2Cl$ in 1 ml of pyridine. After the addition was complete, the reaction mixture was stirred at 25° for 3 hr. The mixture was diluted with ice–H_2O (100 ml) and the precipitate was taken up in Et_2O; the Et_2O was washed (dilute HCl, H_2O), dried (Na_2SO_4), and evaporated. The residue was taken up in 100 ml of EtOH and there was added a tenfold excess of Na_2S dissolved in a minimum amount of H_2O. The mixture was boiled under reflux for 24 hr. The solvent was removed under vacuum and the residue was taken up in Et_2O, washed (H_2O), dried (Na_2SO_4), and evaporated to give 60 mg of a white solid. The protecting ether group was hydrolyzed in 10 ml of EtOH, 3 drops of HCl, and 1 ml of H_2O at 60° for 5 min. The mixture was cooled, evaporated, and extracted with Et_2O to afford a solid (0.050 g). Several recrystallizations from Et_2O–hexane gave the product: mp 180–182°; *m/e* 294.2017 (M^+). *Anal.* Calcd for $C_{18}H_{30}OS$: C, 73.43; H, 10.27. Found: C, 73.80; H, 9.80.

2-Thia-*A*-nor-5α-estran-17-one (14). A solution of 0.2 g of 2-thia-*A*-nor-5α-estran-17β-ol,[2] 1.6 ml of cyclohexanone, and 0.6 g of aluminum isopropoxide in 50 ml of freshly distilled toluene was refluxed for 14 hr. After removing the solvent under vacuum, the residue was treated with 5% hydrochloric acid and the product extracted with ether. After washing with sodium bicarbonate solution and water and drying over sodium sulfate, the solution was evaporated and the oily residue was purified by preparative tlc. Recrystallization from aqueous methanol yielded 0.120 g of product: mp 163–165°. *Anal.* ($C_{16}H_{24}OS$) C, H, S.

17α-Ethyl-2-thia-*A*-nor-5α-estran-17β-ol (15). A solution of 0.06 g of **14** in freshly distilled tetrahydrofuran (10 ml) was added dropwise to 5 ml of ethyllithium (1.29 *M* in benzene) at 0°. After 4 hr of refluxing, starting material was still predominant as shown by tlc and another 5 ml of ethyllithium was added. After additional refluxing for 12 hr, the mixture was worked up by slowly pouring it into ice water, acidified with HCl, and extracting with ether. The residue from evaporation of the solvent was separated on silica gel plates using acetone–petroleum ether (1:10) and recrystallized from acetone–petroleum ether to give 0.005 g of product: mp 194–196°. *Anal.* ($C_{18}H_{30}OS$) C, H.

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Synthesis and Antimalarial Activity of Anthracene Amino Alcohols

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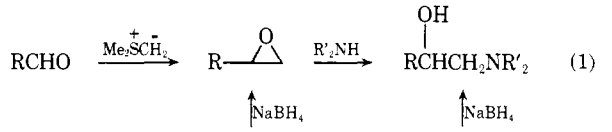
In spite of the consistently high levels of antimalarial activity noted for phenanthrene amino alcohols,[1] the isomeric anthracene amino alcohols have been virtually ignored. The combination of negative biological data and synthetic difficulties afforded little incentive to conduct more than a cursory examination of this class of materials.[2] It was not until 1968 that the first example of an authentic "2 carbon" anthracene amino alcohol was described.[3] Subsequent evaluation noted that the 9-anthracene amino alcohols[4] prepared by Duncan were at least as active against *Plasmodium berghei* infected mice as the analogous 9-phenanthrene amino alcohols.† More recently Huffman[5] reported the synthesis of 10-chloro- and 10-bromo-9-anthracene amino alcohols, with the chlorine exerting the most favorable effect on antimalarial activity. Synthetic difficulties in this ring system apparently thwarted attempts to expand on their observation.

We describe herein our studies of anthracene amino alcohols aimed at a further delineation of activity dependence upon ring positions for (a) the basic amino alcohol side chain and (b) the pharmacophoric chlorine(s). These studies have been restricted to the "2 carbon" amino alcohol side chain terminating in either C_4 or C_7 hydrocarbon fragments because these structural features appear to be preferred in the highly active phenanthrene amino alcohols.[6]

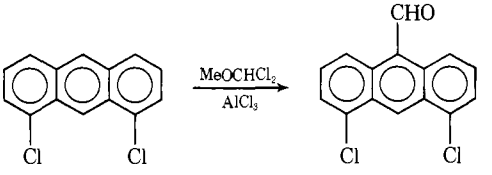
Chemistry. The Duncan[3] technique (sequence 1) for the introduction of the "2 carbon" amino alcohol side chain into aromatics offers obvious synthetic advantages over the more classical procedures. However, difficulties encountered in preparing the unknown chloro-substituted 1- and 2-anthraldehydes impeded its use for obtaining 1- and 2-anthracene amino alcohols. The synthesis of these isomers was realized *via* one of the routes which starts with acid chloride (sequence 2).



With the exception of 3-chloro-1-anthraquinonecarboxylic acid all the intermediate 1- and 2-anthraquinonecarboxylic acids employed in this study were obtained by the procedures detailed in the literature. The direct oxidation of 3-chloro-1-methylanthraquinone with 55% HNO_3 at 200° was found to be a more efficient route to this carboxylic acid than the involved scheme used by Kaimatsu.[7] Oxidation of this methyl group with various chromium or manganese oxidants was ineffectual. The classical Zn-NH_4OH reduction of anthraquinones to anthracenes converted the parent and substituted 1- and 2-anthraquinonecarboxylic acids to the corresponding anthroic acids. It is noteworthy that the integrity of the 4- and 8-position chlorine atoms was maintained during the Zn-NH_4OH reduction of 4,8-dichloro-1-anthraquinonecarboxylic acid. This reductive method is reported to result in the expulsion of chlorine from 4-chloro-1-anthraquinonecarboxylic acid.[8]

Standard techniques for the transformation of the carboxylic acid group to the α-bromomethyl keto function were applicable to the 1- and 2-anthroic acids. Conversion of the bromomethyl ketones to the amino alcohol function was realized through the intermediacy of anthracenyloxiranes and a subsequent ring opening with the appropriate amine, or *via* nucleophilic displacement of bromine by amine, followed by reduction of the resulting α-aminomethyl ketone. This latter sequence has been described as problematic with anthracenes‡ and other aryl systems,[9] because of instability of the α-aminomethyl aryl ketones. However, we have found it to be a perfectly viable route to "2 carbon" 1- and 2-anthracene amino alcohols. The amino alcohols prepared for this work are given in Table I.

Application of reaction sequence 2 to the preparation of 9-anthracene amino alcohol was precluded by the failure of 4,5- or 1,8-dichloro-9-anthroyl chloride to yield the α-bromomethyl ketone *via* the diazomethane route. However, two 9-anthracene amino alcohols, **11** and **12**, were obtained *via* reaction sequence 1. Synthesis of the requisite 4,5-dichloro-9-anthraldehyde was realized with the reagent Gross[10] described for the preparation of the parent 9-anthraldehyde.



This reagent also formylated 1,5-dichloroanthracene in the 9 position. However, all attempts to convert 1,5-dichloro-9-anthraldehyde to the corresponding anthracenyloxirane with various "methylene" transfer reagents were unrewarding. Huffman[5] similarly noted an inhibition of the methylene transfer reaction with certain halogenated 9-anthraldehydes.

Biological Evaluation. All the anthracene amino alcohols listed in Table I, except **7**, were found to be active against *P. berghei* infected mice in the standard Rane[11] activity screen. Compound **12** was the most active material tested, effecting four cures per five test animals at a dosage of 80 mg/kg.

It appears that the structure-activity parameters known to be operative in carbocyclic amino alcohols such as phenanthrenes[2,6] and naphthalenes[2,6] are also significant to the activity of anthracene amino alcohols against *P. berghei*. For example, the levels of activity generally increase with the length of the terminal hydrocarbon fragment and chlorine(s) exerts prominent pharmacophoric effects on the anthracene amino alcohol activity. The lower activity level of the 2-anthracene amino alcohol **4** (compare **4** with

† 9-[1-Hydroxy-2-(di-*n*-heptylamino)ethyl]phenanthrene increased the survival time of the parasitized mice to 9.4 days at 160 mg/kg, 10.4 days at 320 mg/kg, and three curves at 640 mg/kg. Data supplied by R. E. Strube of WRAIR.

‡ 9-(ω-Bromoacetyl)anthracene is reported not to react with secondary amines. See ref 2d.