Thia Steroids. I. 2-Thia-A-nor-5α-androstan-17β-ol, an Active Androgen[1]

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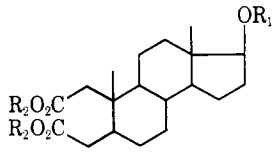
The synthesis of 2-thia-A-nor-5α-androstan-17β-ol as an isostere of 5α-androst-2-ene is described. 17β-Hydroxy-2,3-seco-5α-androstane-2,3-dioic acid is degraded *via* the Barbier–Wieland route to the corresponding bisnor 1,4-dimesylate, or alternatively by a modified Hunsdieker procedure to the bisnor 1,4-dibromide. Cyclization with NaSH gives the thia steroid, which has androgenic activity of the order of testosterone.

In previous studies of modified androstanes based on the hypothesis that sp^2-hybridized carbon atoms at C-2 and/or C-3 are associated with androgenic activity,[2] we introduced various systems having sp^2 geometry at these centers. Thus, the use[3] of epoxide and cyclopropane moieties led to active compounds such as 2α,3α-epoxy-17α-methyl-5α-androstan-17β-ol. Moreover, 2α,3α-episulfides have been shown to be androgenic in other laboratories.[4]

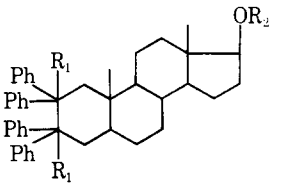
The activity of such compounds indicates that the hypothesis has predictive value, and, in order to subject this to a severe test, the preparation of a suitable noncarbon analog was undertaken. The radicals –CH=CH– and –S– are considered isosteric.[5] This is especially the case when cyclic derivatives are considered, and there are many examples of the similarity of the physical[6] and biological[7] properties of thiophene analogs of benzene compounds. In this study, the preparation of an androstane analog in which sulfur replaced sp^2 centers at C-2 *and* C-3, *i.e.*, a 2-thia-A-nor-5α-androstane derivative, was undertaken.

Only a few thia steroids having sulfur as a hetero atom in one of the four steroid rings have been reported.[8] 3-Thia-5α-cholestane,[9,10] the corresponding sulfoxide, and the related 2-thiaestrane[11] and 2-thiaandrostane[12] derivatives have been described recently. In the case of five-membered rings, until recently only 6-thia-B-norequilenin derivatives[13] and 1-thia-3-aza-A-norandrostane compounds[14] were known, and during the course of this study the synthesis of 2-thia-A-nor-5α-cholestane was reported.[15]

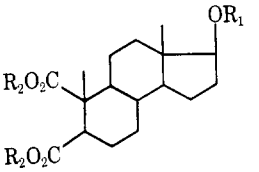
The synthesis of A-northia steroids from conventional steroids requires cleavage of the A ring, removal of two carbon atoms, and the obtainment of a dihalide or the equivalent for the incorporation of sulfur through a cyclization reaction. The first route which was envisaged utilized 17β-hydroxy-1,4-seco-2,3-bisnor-5α-androstane-1,4-dioic acid (**7**), which had not been described in the literature, as an intermediate. Treatment of 17β-hydroxy-2,3-seco-5α-androstane-2,3-dioic acid (**1**)[16] with CH_2N_2 gave crystalline **3**.[17] Barbier–



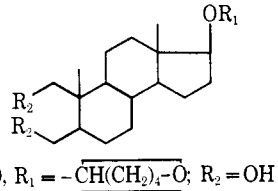
1, $R_1 = H$; $R_2 = H$
2, $R_1 = Ac$; $R_2 = H$
3, $R_1 = H$; $R_2 = CH_3$
4, $R_1 = Ac$; $R_2 = CH_3$



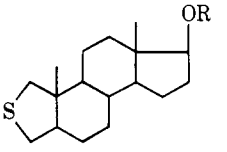
5, $R_1 = OH$; $R_2 = OH$
6, $R_1 = \Delta$; $R_2 = OAc$



7, $R_1 = H$; $R_2 = H$
8, $R_1 = Ac$; $R_2 = CH_3$



9, $R_1 = -\overline{CH(CH_2)_4-O}$; $R_2 = OH$
10, $R_1 = -\overline{CH(CH_2)_4-O}$; $R_2 = OMs$
11, $R_1 = Ac$; $R_2 = Br$



12, R = H
13, R = Ac
14, $R = COC_2H_5$

Wieland degradation of **4** gave tetraphenylcarbinol **5**, which in boiling moist AcOH produced olefin **6**. Cleavage of the double bond in **6** by the customary reagents (O_3, $KMnO_4$, CrO_3) proceeded in poor yield. However, the required compound **7** could be obtained readily through the action of $NaIO_4$ and a catalytic amount of RuO_4[18,19] and subsequent saponification. Diacid **7** was esterified with CH_2N_2 and, after the 17β-hydroxy group was protected as the tetrahydropyranyl ether, the action of LAH gave diol **9**. Formation of mesylate

(1) This investigation was supported in part by a Public Health Service Research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

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10, cyclization in the presence of NaHS, and cleavage of the protecting group gave the desired **12** in 4% over-all yield from **2**.

A much shorter method[15] involving a modified Hunsdiecker reaction[20,21] (49% yield) gave dibromide **11** which could be cyclized with concomitant hydrolysis directly to **12** in 56% over-all yield from **2**.

Discussion

The data from the pharmacological testing[22,23] are displayed in Table I. The free alcohol **12** and the propionate **14** are of comparable activity, whereas the acetate **13** is significantly more active. All parameters measured, including body weight, show increases. On the basis of dose–response data on similar tests on testosterone, the potency of **13** is on the order of testosterone.

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	17.3 ± 1.15	12.9 ± 0.40	23.3 ± 1.49	56	88
Testosterone propionate (0.3)	32.7 ± 4.25	18.4 ± 0.54	31.4 ± 2.31	55	89
p	<0.01	<0.001	<0.02		
Testosterone (0.3)	26.5 ± 1.15	16.8 ± 1.08	23.7 ± 1.67	55	87
p	<0.001	<0.01	NS[b]		
12 (3.0)	46.9 ± 4.18	35.5 ± 3.06	56.8 ± 2.54	55	90
p	<0.001	<0.001	<0.001		
13 (3.0)	61.9 ± 6.04	48.6 ± 3.56	65.2 ± 3.45	55	95
p	<0.001	<0.001	<0.001		
14 (3.0)	49.2 ± 4.46	43.4 ± 1.96	58.9 ± 1.61	55	92
p	<0.001	<0.001	<0.001		

[a] Mean ± standard error. [b] NS = not significant.

Two principal conclusions may be derived from the data. First, the activity of these compounds, having an isosteric system involving neither carbon nor sp^2 bonds, indicates that *steric* effects, and not *electronic* factors, are important in connection with C-2 and/or C-3 in androgens.

Second, it is possible to prepare biologically active nor steroids by substituting –S– for –CH=CH–. It is noteworthy in this connection, that A-nortestosterone is only weakly androgenic.[24] The extension of these studies to a variety of other steroids is in progress.

Experimental Section[25]

17β-Hydroxy-2,3-seco-5α-androstane-2,3-dioic Acid Dimethyl Ester (3).—A solution of 0.050 g of **1** in Et_2O was esterified with CH_2N_2 and, after the usual work-up, 0.045 g of **3** was obtained. Several recrystallizations from hexane gave the analytical sample: mp 85–86°; $[\alpha]^{20}D$ + 5° (*c* 1, $CHCl_3$); nmr, 0.75 (18-H), 0.84 (19-H), and 3.68 ppm (s, 6-OCH_3). *Anal.* ($C_{21}H_{34}O_5$) C, H.

17β-Hydroxy-2,3-seco-5α-androstane-2,3-dioic Acid Acetate Dimethyl Ester (4).—Esterification of 15.0 g of **2** with CH_2N_2 in Et_2O and the usual work-up gave 15.0 g of **4**. Several recrystallizations from MeOH gave the analytical sample: mp 109–110°; $[\alpha]^{20}D$ +2° (*c* 1, $CHCl_3$); nmr, 3.62, 3.65 ppm (2 s, 6). *Anal.* ($C_{23}H_{36}O_6$) C, H.

2,3-Seco-2,2,3,3-tetraphenyl-5α-androstane-2,3,17β-triol (5).—A solution of 4.0 g of **4** in 350 ml of dry Et_2O was added dropwise during 1 hr to a stirred ice-cold solution of 12 ml of 3 *M* C_6H_5MgBr in Et_2O (Arapahoe). The mixture was stirred at 25° for 6 hr and kept for 12 hr. It was cooled in an ice bath and saturated NH_4Cl solution was added slowly until the organic layer became clear. This layer was filtered and the precipitated Mg salts were washed well with Et_2O. The combined organic extracts were steam distilled in order to remove biphenyl. The distillation flask contents were extracted with Et_2O, dried ($MgSO_4$), and evaporated. Tlc showed two major spots, one having the same R_f value as the starting material. The product (7.0 g) was dissolved in Et_2O (300 ml) and the Grignard procedure was repeated. After again working up, crystallization from Et_2O–pentane yielded 5.0 g of **5**, mp 198–201°. Several recrystallizations from the same solvent gave the analytical sample, mp 204–205°, $[\alpha]^{20}D$ −24° (*c* 1, $CHCl_3$). *Anal.* ($C_{43}H_{50}O_3$) C, H.

17β-Hydroxy-2,3-seco-2,2,3,3-tetraphenyl-5α-androsta-2,3-diene Acetate (6).—A mixture of 3.0 g of **5** in 100 ml of glacial AcOH and 2 ml of H_2O was boiled under reflux for 3 hr. Evaporation of the solvent under reduced pressure gave a mixture of **6** and the corresponding 17β-hydroxy derivative. The mixture was acetylated in 15 ml of pyridine and 10 ml of Ac_2O at 25°. After the usual work-up, the product was recrystallized from Et_2O–hexane to give 2.0 g of **6**. Several recrystallizations from the same solvent mixture gave the analytical sample: mp 116–118°; $[\alpha]^{20}D$ −63° (*c* 1, $CHCl_3$); nmr, 5.38 (s, 1) and 6.38 ppm (d, 1, *J* = 10 cps). *Anal.* ($C_{45}H_{48}O_2$) C, H.

17β-Hydroxy-1,4-seco-2,3-bisnor-5α-androstane-1,4-dioic Acid (7).—Compound **8** (0.20 g) was saponified in 5% EtOH–KOH under reflux for 0.5 hr, cooled, poured into H_2O, and acidified with HCl. The precipitate was filtered and recrystallized from EtOAc–MeOH to give 0.15 g of **7**. Several recrystallizations from the same solvent gave the analytical sample, mp 270–271°, $[\alpha]^{20}D$ +14° (*c* 1, 95% EtOH). *Anal.* ($C_{17}H_{26}O_5$) C, H.

17β-Hydroxy-1,4-seco-2,3-bisnor-5α-androstane-1,4-dioic Acid Acetate Dimethyl Ester (8).—A mixture of 1.50 g of $NaIO_4$, 0.20 g of RuO_4, and 30 ml of H_2O was stirred at 0° for 30 min. An additional 1.6 g of $NaIO_4$ was added followed by dropwise addition of 2.0 g of **6** dissolved in 80 ml of cold Me_2CO (distilled from $KMnO_4$). A black precipitate formed immediately. During the next 9 hr at room temperature under stirring, a total of 4.8 g of $NaIO_4$ was added in small portions in order to remove the black precipitate whenever it appeared. Excess RuO_4 was then destroyed by addition of 16 ml of *i*-PrOH. The mixture was added to aqueous NaCl containing 1 ml of 36% HCl and extracted with Et_2O (four 100-ml portions). The combined Et_2O extract

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(25) 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 a field strength of 60 MHz on samples in $CDCl_3$ on a Varian A-60A instrument, using TMS as internal standard. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMU-6D instrument by Morgan-Schaffer Corp., Montreal, Quebec, Canada, or by Mr. William Garland on a MS-902 high-resolution instrument. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. 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.

was washed with H_2O. The product was extracted into saturated $NaHCO_3$ solution which was then acidified with HCl and extracted with Et_2O. Evaporation of the dried (Na_2SO_4) Et_2O gave 0.65 g of the 17β-hydroxy-1,4-seco-5α-androstane-1,4-dioic acid acetate which was esterified with CH_2N_2 to give **8**. Recrystallization from MeOH gave 0.50 g of **8**. Several recrystallizations from MeOH furnished the analytical sample: mp 116–118°; $[\alpha]^{20}D$ −26° (*c* 1, $CHCl_3$); nmr 3.62 and 3.7 ppm (6 H, 2-OCH_3). *Anal.* ($C_{21}H_{32}O_6$) C, H.

1,4-Seco-2,3-bisnor-5α-androstane-1,4,17β-triol 17-(2′-Tetrahydropyranyl) Ether (9).—Compound **7** was treated with CH_2N_2 in Et_2O to give the corresponding dimethyl ester, as indicated by the nmr spectrum: 0.72 (s, 18-H), 1.12 (s, 19-H), 3.62 and 3.73 ppm (s, s, 3, 3, OCH_3). A solution of 0.5 g of the dimethyl ester in 50 ml of dry dihydropyran and a drop of $POCl_3$ was stirred at room temperature for 1 hr and evaporated under reduced pressure. The residue was dissolved in ether, washed ($NaHCO_3$ solution, H_2O), dried (Na_2SO_4), and evaporated to give the crude tetrahydropyranyl ether, as indicated by the nmr spectrum: 0.78 (s, 3, 18-H), 1.12 (s, 3, 19-H), 3.62 and 3.70 ppm (s, s, 3, 3, OCH_3).

This tetrahydropyranyl ether (0.25 g) was dissolved in 50 ml of dry Et_2O and added to 0.5 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 saturated solution of sodium potassium tartrate was carefully added, and the mixture was filtered. The precipitate was washed with Et_2O, and the combined Et_2O solution was washed (dilute HCl, H_2O), dried (Na_2SO_4), and evaporated. The residue was crystallized several times from Me_2CO giving colorless crystals, mp 158–160°. *Anal.* ($C_{32}H_{38}O_4$) C, H.

1,4-Seco-5α-androstane-1,4,17β-triol 1,4-Dimethanesulfonate 17-(2′-Tetrahydropyranyl) Ether (10).—To a cold solution of 0.16 g of **9** in 3 ml of pyridine was added dropwise with stirring, a cold solution of 0.15 g of $MeSO_2Cl$ in 0.5 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 filtered and washed (H_2O). It was recrystallized from Et_2O–petroleum ether (bp 30–60°) to give 0.17 g of **10**. Several recrystallizations from the same solvent gave the analytical sample: mp 114–116°; nmr, 0.77 (s, 3, 18-H), 0.84 (s, 3, 19-H), 3.4 and 3.5 ppm (2 s, 6, SO_2CH_3). *Anal.* ($C_{24}H_{42}O_8S_2$) C, H, S.

1,4-Dibromo-1,4-seco-2,3-bisnor-5α-androstan-17β-ol Acetate (11).—To 1.9 g of **2** in 100 ml of stirred, refluxing CCl_4, there was added 1.62 g of red HgO. The reaction mixture was shielded from light, and Br_2 (1.6 g) was added dropwise. After 1.5 hr, the reaction mixture was allowed to cool, the dark mixture was filtered, and the filtrate was concentrated under vacuum. The residue was chromatographed on Al_2O_3 to give 1.1 g of pure **11** which was recrystallized from MeOH; mp 155–158°, $[\alpha]^{20}D$ −2° (*c* 1, $CHCl_3$). *Anal.* ($C_{19}H_{30}Br_2O_2$) C, H, Br.

2-Thia-A-nor-5α-androstan-17β-ol (12). Procedure A.—A solution of NaHS was prepared by bubbling H_2S into a suspension of 9 g of NaOMe in 70 ml of $HOCH_2CH_2OEt$ until the exothermic reaction ceased. The resulting mixture was filtered and to 30 ml there was added 0.10 g of **10**. The mixture was heated at reflux for 20 min, cooled, and diluted with H_2O. The precipitated product was collected and dried. 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 analytical sample, mp 141–143°, $[\alpha]^{20}D$ +58°, m^+ = 280. *Anal.* ($C_{17}H_{28}OS$) C, H, S.

Procedure B.—A solution of 0.10 g of **10**, 100 ml of 80% EtOH, and 300 mg of NaS was heated at reflux for 6 hr. After cooling, it was worked up as in procedure A to afford **12**, mp 141-143°.

Procedure C.—To a refluxing solution of 0.70 g of **11** in 100 ml of refluxing EtOH there was added a tenfold excess of NaSH dissolved in the minimum amount of H_2O. Heating was continued for 24 hr when tlc indicated complete conversion of the dibromide to the product. 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 0.50 g of **12** as a white solid.

2-Thia-A-nor-5α-androstan-17β-ol Acetate (13).—A solution of 0.05 g of **12** in 2 ml of pyridine and 1 ml of Ac_2O was kept overnight at 25°, poured into 20 ml of ice–H_2O, acidified to pH 3, and extracted with Et_2O. The Et_2O was washed several times with H_2O, dried (Na_2O_4), and evaporated to give an oil which was purified by preparative tlc on silica gel to give **13** as an oil soluble in all organic solvents. On drying under vacuum, it crystallized giving a solid which was crystallized from petroleum ether at −70° giving crystals, mp 88–89°, $[\alpha]^{20}D$ +50° (*c* 1, $CHCl_3$), m^+ = 322. *Anal.* ($C_{19}H_{30}O_2S$) C, H, S.

2-Thia-A-nor-5α-androstan-17β-ol Propionate (14).—A solution of 0.05 g of **12** in 2 ml of pyridine was treated with 1 ml of $(EtCO)_2O$. It was worked up as in the case of **13**, giving a solid, mp 88–90°, $[\alpha]^{20}D$ 64° (*c* 1, $CHCl_3$), m^+ = 336. *Anal.* ($C_{20}H_{32}O_2S$) C, H, S.

The Synthesis and Progestational Activity of Some 1,2α-Cyclomethylene-16-methylene Progesterone Derivatives

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The progestational activities and syntheses of the 1,2α-cyclomethylene-16-methylene compounds **4**, **15**, and **25** and of the precursor 1,4,6-trienes **26**, **16**, and **23** are reported. In all cases the trienes exhibited higher progestational activity than the corresponding 1,2α-cyclomethylene derivatives when tested intramuscularly in the rabbit.

The progestational potentiating effect of the 16-methylene moiety has been described.[2] Recently, progesterone analogs have been reported which have a 1,2α-cyclomethylene moiety.[3,4] We felt it to be of biological interest to combine these two structural features in the same molecule and now report some of our findings with compounds of this type. Specifically, we have synthesized 1,2α-cyclomethylene-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**4**), 1,2α-cyclomethylene-6-methyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**15**), and 1,2α-cyclomethylene-16-methylene-6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**25**).

The synthesis of the 1,2α-cyclomethylene **4** (Scheme

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