Journal of Medicinal Chemistry

VOLUME 12, No. 1 DECEMBER 26, 1968

17-(5-Substituted 2-Thienyl) and 17-(5-Substituted 2-Thienylidene) Derivatives of Selected 17-Keto Steroids[1,2]

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Received May 24, 1968
Revised Manuscript Received August 12, 1968

The reaction of 5-methoxy-2-thienyllithium with 3β-hydroxy-5α-androstan-17-one, androsterone, estrone, and 3β-hydroxyandrost-5-en-17-one has led to the diols (Scheme I). Mild acid treatment produced the ring D olefins **3**; more drastic hydrolysis led to the substituted 2(5H)-thiophenone derivatives as geometric isomers **4**. Incomplete biological tests have shown no important physiological action although **4a** and **4c** did increase contractile force, heart rate, and blood pressure in dogs; it was concluded that the activity was probably due to release of endogenous norepinephrine from cardiac sympathetic nerve endings.

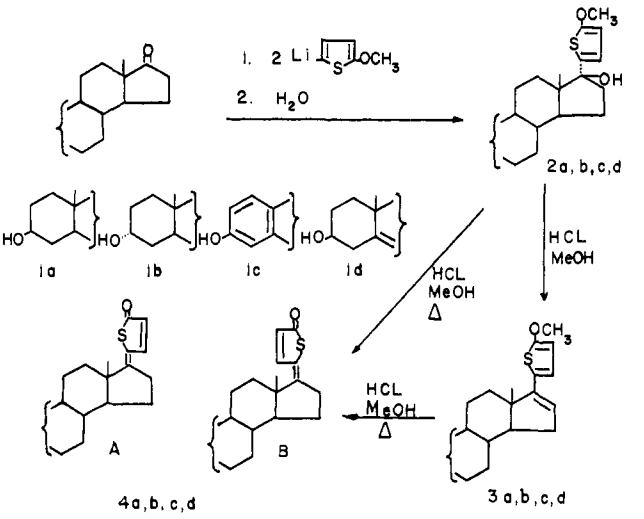
In earlier work we have described a general method for the introduction of the 5-substituted 2(5H)-thiophenone moiety at the site of a carbonyl group.[3] The basic reaction involves the treatment of a ketone (or aldehyde) with 5-methoxy-2-thienyllithium followed by acid hydrolysis. We now wish to report a series of 17-steroidal thiophene and 2(5H)-thiophenone derivatives which have been prepared by this method for biological screening.

The reactions starting with 3β-hydroxy-5α-androstan-17-one (**1a**), androsterone (**1b**), estrone (**1c**), and 3β-hydroxyandrost-5-en-17-one (**1d**) are summarized in Scheme I.

As an example, when **1a** was treated with a 2 molar excess of 5-methoxy-2-thienyllithium in THF–hexane solution, the solid lithium salt of the diol **2a** separated and upon careful addition of water was converted to the free diol in 60% over-all yield. When the lithium salt was treated briefly at room temperature with MeOH–dilute HCl, the ring D olefin **3a** was produced (53% from **1a**). When either the diol **2a** or the olefin **3a** was refluxed for 30 min with MeOH–HCl, the mixed geometric isomers of **4a** were obtained (83% from **2a** and 69% from **3a**). Although isomers **4a** (A and B) were not usually separated, evidence for their presence was found in the nmr spectra.

The diol **2d** was also prepared by treating the corresponding lithium salt with water; however, a purer product was obtained when anhydrous methanol was added to the lithium salt. The diol **2d** was converted

SCHEME I



to the ring D olefin **3d** by mild acid treatment and to the testosterone derivative **6** by Oppenauer oxidation. A similar oxidation of thiolactone **4d** led to the Δ^4-keto thiolactone **5** (Scheme II).

Structural assignments were based upon ir, uv, and nmr data. The diols **2** in addition to absorption at 3530 and 3370 cm^{-1} (hydroxyl) exhibited absorption at 1500 cm^{-1}, characteristic of substituted thiophene, and at 1208 and 1234 cm^{-1}, consistent with the 2-methoxythienyl group.[4] The hydroxyl at C-17 is tentatively shown in the β configuration although direct evidence has not been obtained. As would be anticipated, the spectra of the diols were similar to those of the respective ring D olefins **3** although a strong band at 1540 cm^{-1}, probably due to the C-16 double bond, was observed for the olefins; the diols produced a much

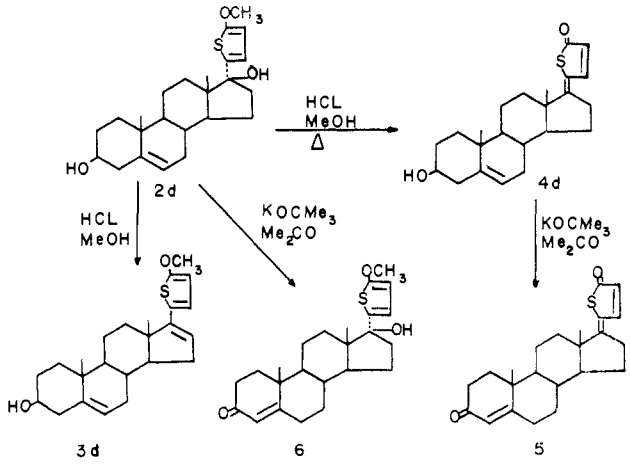
(1) This investigation was supported by Public Health Service Research Grant CA 06774, from the National Cancer Institute.

(2) Presented in part before the Division of Medicinal Chemistry, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract No. P26.

(3) (a) W. R. Biggerstaff and K. L. Stevens, *J. Org. Chem.*, **28**, 733 (1963); (b) W. R. Biggerstaff, H. Arzoumanian, and K. L. Stevens, *J. Med. Chem.*, **7**, 110 (1964).

(4) S. Gronowitz, *Advan. Heterocyclic Chem.*, **1**, 1 (1963); see p 12.

Scheme II



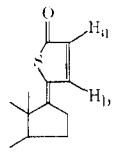
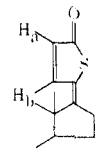
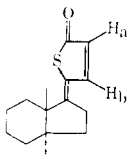
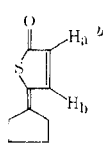
weaker absorption in this region. Absorption differences in the uv region were striking; the diols absorbed at 254 mμ, whereas the conjugated olefins absorbed at 297 mμ.

Evidence in the ir region for the α,β-unsaturated thiolactone structure was found in the absence of bands associated with the 2-methoxythienyl group and the presence of a strong band at 1673 cm^{-1} produced by the α,β-unsaturated carbonyl group. Absorptions characteristic of a conjugated carbon–carbon double bond system were observed at 1608 and 1555 cm^{-1}. The uv spectra of the thiolactones **4** showed absorption at 325–328 mμ. The α,β-unsaturated keto thiolactone **5**, however, showed bands at 239 and 328 mμ consistent with the two chromophoric groups.

A study of the nmr spectra of the thiolactones led to the chemical shift data recorded in Table I. As might be expected, a mutual deshielding interaction occurred between the thiolactone proton H_b and the protons of the 18-methyl group in the series B geometric isomers. In the case of the A isomers, the proton H_b was usually affected only slightly; a marked exception, however, was the thiolactone pair (**4c**), obtained from estrone, in which case both isomers A and B exhibited strong downfield shifts of the H_a and H_b doublets. The assignments of the H_a and H_b doublets were based upon the δ values obtained for the reference compound, 5-cyclopentylidene-2 (5H)-thiophenone. The correlation of the two vinyl doublets produced by each isomer with its 18-methyl peak was accomplished by comparing integration ratios of the isomer A and B H_b doublets with the ratios of the two 18-methyl peaks. Since only

Table I

Nmr Data for Substituted 2(5H)-Thiophenones

	δ, ppm				
					
Compd	A	B	18-H	19-H	$J_{3,4}$, cps
4a	H_a 6.23 H_b 7.73		0.97	0.83	6.0
		H_a 6.23 H_b 7.97	1.05		
4b		H_a 6.24 H_b 7.91	0.92	0.75[a]	6.0
4c	H_a 7.06 H_b 8.02		0.94		6.0
		H_a 7.06 H_b 8.20	1.03		
4d	H_a 6.25 H_b 7.70		1.02	1.07	6.0
		H_a 6.25 H_b 7.96	1.09		
5	H_a 6.25 H_b 7.75		1.00	1.21[a]	6.0
 or B[c]	H_a 6.17 H_b 7.69		(H-8), 0.96		6.0
		H_a 6.18 H_b 7.92	1.05		
 6.24 7.69					
5a-Androstone			0.692	0.792	

[a] Agrees with calculated value; see ref 5. [b] Prepared for reference by H. S. Uh of our laboratory (unpublished). [c] Prepared by H. Dam (unpublished).

single isomers were observed for **4b** and **5**, the assignments in these two instances, of the 18-H and 19-H peaks, could not be made by this method. Tentative selections of the 19-H peaks (and hence the 18-H values) were based upon the effects of steroid substituents on the chemical shift compiled by Zürcher.[5] The coupling constant $J_{3,4}$ = 6.0 cps was in agreement with previously reported values for the 2(5H)-thiophenone protons.[6] The nmr data for related compounds are included in the Experimental Section.

Biological Evaluation.—Although biological testing of our compounds is incomplete, the following results are available: estrogenic action on the ovariectomized mouse was negative for compounds **4a**, **4b**, **2a**, **3a**, and **3b** when injected subcutaneously at a rate of 2 mg daily for 5 days. The test used was that of the uterine weight of the mouse compared with the effect produced by a total dose of 0.25 μg of estrone. Compound **4c** was *ca.* $^1/_{400}$ × estrone in activity. None of the compounds indicated antiestrogenic effects when added to a one-half maximal dose of estrone, *i.e.*, the uterine weight was neither augmented nor depressed.[7a]

A screening test of **4c** with tissue culture KB, human epidermoid carcinoma of the nasopharynx, was negative. Compounds **4a**, **4b**, and **4c** administered intraperitoneally (400 mg/kg) daily to mice bearing L1210 lymphoid leukemia failed to prolong the life span.[7b]

Dr. Neil C. Moran, Department of Pharmacology, Emory University, has evaluated the cardiotonic action of selected thiobutenolides. Compounds **4a**, **4b**, and **4c** were tested on the isolated rabbit atrium; in one experiment **4a** increased contractile force at 2 and 4 μg/ml; 8 and 16 μg/ml depressed the heart. In another experiment 1, 2, and 4 μg/ml had no effect, 8 μg/ml increased contractile force, and 16 and 32 μg/ml depressed the force. In one experiment with compounds **4b** and **4c**, stimulation was observed at 1 and 2 μg/ml and depression at 4, 8, and 16 μg/ml. Increases in force of contraction were accompanied by no alteration in rhythm. Doses of 1, 2, 4, 8, 16, and 32 μg/ml were administered cumulatively in geometric progression; in only one experiment (**4a**) was 32 μg/ml used; all others stopped at 16 (cumulative = 31 μg/ml). Following the administration of the test compounds (total, 31 μg/ml) in the muscle bath, ouabain was given, producing typical myocardial stimulant effects in each instance, except following **4a**, where ouabain failed to increase contractile force in two experiments. In all experiments, including the two with **4a**, ouabain caused rhythm disturbances (*i.e.*, a toxic effect) at a concentration of 3 μg/ml. It was concluded that none of the four compounds had antiglycoside action.

The cardiac stimulant action of **4a** was evaluated in two dogs. In the first, when administered intravenously in increments (10, 20, 40, 80, 160, 320, and 640 μg/kg) it produced an initial effect seen at 80 μg/kg (cumulative = 150 μg/kg); a marked increase (100%) of contractile force, heart rate, and blood pressure was seen at 160 μg/kg (cumulative = 310 μg/kg). The effects were persistent (in contrast to the 2–5-min duration of the effect of epinephrine in this preparation). A total of 1.25 mg/kg iv, given as a series of geometrically increasing doses, failed to produce significant changes in the electrocardiogram. After this dose, a *small* dose of ouabain (45 μg/kg) produced further increase in contractile force and then disturbed rhythm (*e.g.*, cardiotoxicity). This experiment confirmed the ones on the isolated rabbit atrium that **4a** has no antiglycoside activity. The character of the cardiac stimulation suggested an adrenergic mechanism. This was confirmed in a second dog in which the β-adrenergic blocking drug, propranolol, 0.5 mg/kg, prevented the effects of a cumulative dose of 1.5 mg/kg of **4a**. It is most likely that **4a** and **4c** augment contractile force by a form of adrenergic stimulation, perhaps due to release of endogenous norepinephrine from cardiac sympathetic nerve endings.

Experimental Section[8]

17-(5-Methoxy-2-thienyl)-5α-androstane-3β,17ξ-diol (2a).—Into a dried flask were introduced 50 ml of anhydrous THF, 18.8 ml (0.031 mole) of 1.66 *M* *n*-butyllithium–hexane solution (Foote Mineral Co., New Johnsonville, Tenn.), and 3.5 ml (0.035 mole) of 2-methoxythiophene while dry nitrogen[9] slowly passed through the apparatus. The solution was stirred for 1 hr at room temperature during which time it became yellow. A solution of 3.00 g (0.0103 mole) of 3β-hydroxy-5α-androstan-17-one in 50 ml of anhydrous THF was added dropwise to the Li reagent with effective stirring. The resulting light yellow suspension was refluxed with stirring for 6 hr, after which time the solvent was evaporated to dryness in a stream of dry, oxygen-free N_2 and then *in vacuo*. The remaining light yellow powder was treated with 100 ml of H_2O and extracted with three 200-ml portions of $CHCl_3$. The combined extracts were washed three times with H_2O, and dried (Na_2SO_4). Evaporation of the solvent left a light brown solid which weighed 4.66 g after drying *in vacuo*. Recrystallization from $CHCl_3$ gave, in three crops, 2.32 g (55.6%) of colorless crystalline diol **2a**, mp 164–172°. The residue obtained upon evaporation of the filtrate was refluxed for 30 min in 100 ml of MeOH and 25 ml of 1 *N* HCl. The reaction mixture was then diluted with 100 ml of H_2O and extracted (Et_2O); the Et_2O layer was washed with 5% Na_2CO_3, H_2O, and dried (Na_2SO_4). The dried residue obtained upon evaporation of the solvent was refluxed for 30 min in 50 ml of EtOH containing 10% AcOH and 1.5 g of Girard's reagent T. The reaction mixture was cooled to room temperature and diluted with 50 ml of H_2O; the aqueous solution containing the Girard derivative of the starting steroid was clarified, acidified with HCl, and warmed briefly to effect hydrolysis. The regenerated ketonic material was then recovered by ether extraction. Crystallization from MeOH–petroleum ether (bp 30–60°) gave 0.24 g of unreacted **1a**; the yield of the diol **2a** was then 60.4%, based on unrecovered steroid.

Further recrystallization of the diol from $CHCl_3$–ether gave the analytical sample: mp 174–176°; $[\alpha]^{24}D$ +45.6°; $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3550 (OH), 1549 (conjugated C=C), 1492 and 1428 (thiophene ring), 1233–1198 (2-methoxythienyl); λ_{max}^{EtOH} 258 mμ (log ε 3.80). The sample was then dried at 0.1 mm for 6 hr at 100°. *Anal.* ($C_{24}H_{36}O_3S$)C, H.

17-(5-Methoxy-2-thienyl)-5α-androst-16-en-3β-ol (3a).—The diol prepared from 4.00 g of **1a** was dissolved in 100 ml of MeOH and treated with 30 ml of 1 *N* HCl for 10 min at room temperature. The solution was diluted to *ca.* 400 ml with H_2O and extracted (Et_2O). The ether layer was washed with 5% Na_2CO_3 and H_2O and dried (Na_2SO_4). The yellow solid obtained upon

(5) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 19.

(6) A.-B. Hörnfeldt, *Arkiv Kemi*, **22**, 211 (1964).

(7) (a) Estrogenic and antiestrogenic tests were supervised by Dr. Roy Hertz, Endocrinology Branch of the National Cancer Institute. (b) The tests were conducted by the Cancer Chemotherapy National Service Center, under the Direction of Dr. Harry B. Wood.

(8) The melting points of samples below 200° were determined on a Hershberg apparatus; those melting above 200° were determined on a Kofler micro hot stage and are corrected. Ir spectra were determined on either a Beckman IR-5 or an IR-12 spectrophotometer. Uv spectra were obtained in 95% EtOH by means of a Beckman DK-2 spectrophotometer. Nmr spectra were determined on a Varian 60 spectrometer using $CDCl_3$ and Me_4Si.

(9) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 219.

evaporation of the ether was recrystallized from MeOH to give 2.81 g (53.5%) of the Δ^{16} derivative **3a** in two crops: a first crop, 2.32 g, mp 145–154°, and a second crop, 0.49 g, mp 129–139°. Recrystallization from MeOH gave an analytical sample as colorless leaflets: mp 156–157°; $[\alpha]^{20}D$ +51.8°; λ_{max}^{EtOH} 297 mμ (log ε 4.08); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3550 (OH), 1540 (conjugated C=C), 1485 (substituted thiophene), 1233 and 1198 (2-methoxythienyl); nmr, δ 0.85 and 0.97 (H-18 or H-19), 3.88 (OCH_3), 5.75 (H-16), 6.05 and 6.64 (thienyl H_3 and H_4) ($J_{3,4}$ = 3.9 cps).[10] The sample was dried (0.1 mm) for 45 hr at 118°. *Anal.* ($C_{24}H_{34}O_2S$) C, H.

3β-Hydroxy-γ-mercapto-5α-androstane-Δ$^{17,\gamma}$-crotonic Acid γ-Lactone (4a) from the Demethylation of 3a.—A solution of the ring D olefin **3a** in 5 ml of MeOH and 1 ml of 1 *N* HCl was refluxed for 30 min; *ca.* 30 ml of H_2O was added and the MeOH was evaporated under vacuum. The aqueous solution was extracted with three 20-ml portions of Et_2O, and the ether solutions were combined, washed (5% Na_2CO_3, H_2O), and then dried (Na_2SO_4). The product was obtained as a solid (52 mg) which was recrystallized from PhH–petroleum ether (bp 30–60°) to give 33 mg (69%) of thiolactone **4a** in three crops, mp 200–210°. Further recrystallization (PhH) gave the pure thiolactone as colorless needles, mp 205–215°. An identical product was obtained when the diol **2a** was treated in a similar manner. When 2.32 g (0.00574 mole) of the diol **2a** was refluxed with 200 ml of MeOH and 50 ml of 1 *N* HCl for 30 min, a solid was obtained which was recrystallized from PhH–petroleum ether (bp 30–60°) to give 0.82 g (38%) of the isomeric thiolactones **4a** (A and B) as colorless needles: mp 218–221°; $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3620 (OH), 1670 (α,β-unsaturated carbonyl), 1630 and 1570 (conjugated C=C). Further recrystallization of the thiolactone from MeOH gave the analytical sample: mp 230–231.5°; $[\alpha]^{24}D$ +39.5°; λ_{max}^{EtOH} 325 mμ (log ε 4.28); nmr, Table I. *Anal.* ($C_{23}H_{32}O_2S$) C, H.

Recrystallization from MeOH of the residue obtained from the foregoing PhH–petroleum ether filtrate gave 0.95 g (45%) of additional hydrated thiolactone, mp 110–117°. Further recrystallization gave the analytically pure thiolactone **4a** (A and B) as the monohydrate in the form of light yellow blades which exhibited a dual melting point, 116–119° and 172–176°. The ir spectrum was nearly identical with that of the anhydrous, mp 231.5°, sample. The nmr spectrum confirmed that this fraction was also **4a** (A and B). *Anal.* ($C_{23}H_{32}O_2S \cdot H_2O$) C, H.

In other runs thiolactone **4a** was prepared from **1a** without isolation of the diol **2a**. Direct treatment of the product from the organolithium reaction with hot methanolic HCl gave **4a** in an over-all yield of 42% (based on unrecovered steroid).

17-(5-Methoxy-2-thienyl)-5α-androst-16-en-3α-ol (3b).—A solution of 2.00 g (0.0069 mole) of androsterone in THF was treated with 5-methoxy-2-thienyllithium (0.0207 mole) in 50 ml of anhydrous THF according to the procedure described for **2a**; the product, after reaction with H_2O, weighed 2.62 g; ir analysis indicated that some diol was present; however, an attempt to isolate the crystalline diol from MeOH gave instead 1.14 g (42.9%) of the ring D olefin **3b** in two crops: 0.96 g, mp 172–174°, and 0.18 g, mp 158–166°. Several recrystallizations from MeOH gave an analytical sample as fine colorless needles: mp 179–180°; $[\alpha]^{24}D$ +52.4°; ν_{max}^{KBr} (cm^{-1}) 3310 (OH), 1530 (conjugated C=C), 1485 (substituted thiophene), 1233 and 1198 (2-methoxythienyl); nmr, δ 0.84 and 0.99 (H-18 or H-19), 3.88 (OCH_3), 5.75 (H-16), 6.05 and 6.65 (thienyl H_3 and H_4) ($J_{3,4}$ = 3.9 cps.). *Anal.* ($C_{23}H_{34}O_2S$) C, H.

3α-Hydroxy-γ-mercapto-5α-androstane-Δ$^{17,\gamma}$-crotonic Acid γ-Lactone (4b, Mixed Isomers A and B) from the Demethylation of 3b.—A solution of 0.44 g of ring D olefin (**3b**) in 80 ml of MeOH and 10 ml of 1 *N* HCl was refluxed for 30 min, cooled, diluted with 200 ml of H_2O, and extracted (Et_2O). The ether layer was washed with 5% $NaHCO_3$ and H_2O and dried (Na_2SO_4). Evaporation left 0.40 g of a solid which was recrystallized (PhH) to yield 0.246 g (58.3%) of thiolactone **4b**, mp 204–268°. An additional 0.064 g (11%) of material, mp 173–188°, was obtained from MeOH.

Recrystallization (PhH) gave the analytical sample in the form of colorless leaflets: mp 263–269°; ν_{max}^{KBr} (cm^{-1}) 3550 (OH), 1665 (α,β-unsaturated carbonyl), 1610 and 1550 (conjugated C=C); nmr, Table I. *Anal.* ($C_{23}H_{32}O_2S$) C, H.

The isomeric thiolactones were also prepared by treating the diol in the initial reaction mixture directly with MeOH–HCl followed by separation of unreacted androsterone (32.3%) with Girard's reagent T. The yield of **4b** (isomers A and B) was 40% based on unrecovered androsterone.

17-(5-Methoxy-2-thienyl)estra-1,3,5(10)-triene-3,17ξ-diol (2c).—Addition of 2.00 g (0.007 mole) of estrone, dissolved in 50 ml of anhydrous THF, to a solution of 5-methoxy-2-thienyllithium (0.019 mole) in 50 ml of anhydrous THF according to the procedure described for **2a** led, after treatment with H_2O, to 3.26 g of a brown solid. Recrystallization from $CHCl_3$ gave 2.73 g of diol **2c**, mp 165–215°. A second recrystallization ($CHCl_3$) gave 2.11 g (74.2%) of colorless **2c**, mp 165–169°. Unreacted estrone (0.21 g) was recovered from the filtrate with Girard's reagent T bringing the yield of the diol to 82.9% based on unrecovered steroid. Further recrystallization of the diol ($CHCl_3$) gave the analytical sample: mp 171–172°; ν_{max}^{KBr} (cm^{-1}) 3480 and 3310 (OH), 1620, 1575 and 1492 (aromatic), 1535 (conjugated C=C), 1200 (2-methoxythienyl). Upon standing, the diol **2c** slowly changed to the Δ^{16} compound **3c**. *Anal.* ($C_{23}H_{28}O_2S$) C, H.

17-(5-Methoxy-2-thienyl)estra-1,3,5(10),16-tetraen-3-ol (3c) from Dehydration of 2c.—A suspension of 1.00 g of diol **2c** in 50 ml of MeOH and 5 ml of 1 *N* HCl was stirred at room temperature for 10 min; during this time the diol slowly dissolved followed by precipitation of the dehydration product in the form of fine needles. The precipitate was filtered, washed (H_2O, 5% $NaHCO_3$), and dried *in vacuo*. Recrystallization (MeOH) gave 0.81 g (85%) of the ring D olefin **3c** as colorless needles, mp 160–163°. Further recrystallization gave an analytical sample: mp 163–164°; ν_{max}^{KBr} (cm^{-1}) 3390 (OH) and 1198 (2-methoxythienyl); nmr, δ 1.00 (H-18), 3.88 (OCH_3), 5.79 (H-16), 6.07 and 6.69 (thienyl H_3 and H_4) ($J_{3,4}$ = 3.9 cps). *Anal.* ($C_{23}H_{28}O_2S$) C, H.

3-Hydroxy-γ-mercaptoestra-1,3,5(10)-triene-Δ$^{17,\gamma}$-crotonic Acid γ-Lactone (4c, Isomers A and B).—A mixture of 0.73 g of **3c** in 50 ml of MeOH and 5 ml of 1 *N* HCl was refluxed for 30 min. During this time **3c** dissolved and the thiolactone **4c** slowly precipitated; the product was filtered, washed, dried, and recrystallized ($CHCl_3$) to give 0.61 g (87%) of **4c**, mp 248–269°. Further recrystallization gave an analytical sample as colorless microcrystals: mp 247–253°; $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3550 (OH), 1665 (α,β-unsaturated carbonyl), 1605 and 1548 (conjugated C=C), 1580 and 1492 (aromatic); nmr, Table I. *Anal.* ($C_{22}H_{24}O_2S$) C, H.

17-(5-Methoxy-2-thienyl)androst-5-ene-3β,17ξ-diol (2d).—When 15.00 g (0.052 mole) of 3β-hydroxyandrost-5-en-17-one dissolved in 180 ml of anhydrous THF was added to 5-methoxy-2-thienyllithium (0.155 mole) under N_2,[9] a tan suspension resulted which was refluxed with stirring for 6 hr. Removal of the solvent left a light brown powder which was treated with H_2O and extracted ($CHCl_3$). After drying (Na_2SO_4), the solution was concentrated and petroleum ether (bp 30–60°) was added. The diol **2d**, 15.2 g (72%), crystallized in two crops, mp 89–102°.

A purer product was obtained in another run by suspending the dry Li salt (from 2.0 g of **1d**) in anhydrous, peroxide-free Et_2O followed by the addition of 2 ml of anhydrous MeOH. The mixture was stirred for 0.5 hr and filtered, and the ether was replaced with $CHCl_3$. Concentration of the solution yielded 1.64 g (78%) of diol **2d**, mp 90–96°.

Further recrystallization ($CHCl_3$) gave an analytical sample: mp 93–97°; $[\alpha]^{25}D$ −22.43; λ_{max}^{EtOH} 254 mμ (log ε 4.88); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 1500 (substituted thiophene), 1208 and 1234 (2-methoxythienyl); nmr, δ 1.01 (superimposed H-18 and H-19), 3.88 (CH_3O), 5.4 (H-6), 6.06 and 6.43 (thienyl H_3 and H_4) ($J_{3,4}$ = 3.9 cps). The diol slowly converted to the olefin **3d** upon standing. *Anal.* ($C_{23}H_{34}O_3S$) C, H.

17-(5-Methoxy-2-thienyl)androsta-5,16-dien-3β-ol (3d).—Treatment of 950 mg of diol **2d** in 50 ml of MeOH and 5 ml of 1 *N* HCl for 5 min led to 878 mg of cream-colored crystals which were washed (H_2O) and recrystallized (MeOH) to yield in two crops 717 mg (79%) of **3d**, mp 148–159°. Further recrystallization gave the analytical sample: mp 155–158°; $[\alpha]^{28}D$ −43.83; λ_{max}^{EtOH} 297 mμ (log ε 4.07); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 1208 and 1234 (2-methoxythienyl); nmr, δ 1.01 and 1.09 (H-18 or H-19), 3.88 (CH_3O), 5.4 (H-6), 5.8 (H-16), 6.06 and 6.68 (thienyl H_3 and H_4) ($J_{3,4}$ = 3.9 cps). *Anal.* ($C_{24}H_{32}O_2S$) C, H.

3β-Hydroxy-γ-mercaptoandrost-5-ene-Δ$^{17,\gamma}$-crotonic Acid γ-Lactone (4d).—A solution of 2.5 g of diol (**2d**) in 200 ml of MeOH and 50 ml of 1 *N* HCl was refluxed for 30 min, diluted with H_2O (200 ml), concentrated to *ca.* 200 ml, and then extracted with three 100-ml portions of $CHCl_3$. The combined $CHCl_3$ solution was washed (5% $NaHCO_3$, H_2O) and dried (Na_2SO_4). Evaporation of the solvent left a solid which was recrystallized (MeOH)

(10) See ref 4, p 8.

to yield 2.17 g (95%) of **4d** (A and B), mp 228–245°. When the thiolactone **4d** was chromatographed on silica gel using a 1:1 mixture of $CHCl_3$–petroleum ether (bp 30–60°) for elution, followed by recrystallization of the main fraction from MeOH, an analytical sample was obtained: mp 247–254°; $[\alpha]^{23}D$ −70.23; λ_{max}^{EtOH} 325 mμ (log ε 4.20); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3610 (OH), 1673 (conjugated C=C); nmr, Table I. *Anal.* ($C_{23}H_{30}O_2S$), C, H.

17ξ-Hydroxy-17-(5-methoxy-2-thienyl)androst-4-en-3-one (6).—In a three-necked flask under N_2, 1 g (0.0025 mole) of diol **2d** in 25 ml of PhH was added, and the mixture was brought to reflux temperature while stirring. To the refluxing mixture 1.00 g of dry, recrystallized Al(O-*i*-Pr)$_3$ and 6 ml of Me_2CO (dried over $MgSO_4$) were added; the mixture was then refluxed with stirring for 19 hr. At the end of the reflux period enough PhH was added to bring the total volume to 100 ml; the solution was then washed with eight 30-ml portions of a 15% solution of potassium sodium tartrate followed by four 30-ml portions of H_2O, and finally concentrated to give a crystalline product (square plates) which was recrystallized (PhH) to yield 0.616 g (61%) of **6**, mp 87–98°. Further recrystallization (PhH) gave an analytical sample: mp 95–101°; $[\alpha]^{23}D$ −46.22; λ_{max}^{EtOH} 251 mμ (log ε 4.30); $\nu_{max}^{CHCl_3}$ 3610 (OH), 1660 (conjugated C=O), 1208 and 1234 cm^{-1} (2-methoxythienyl). *Anal.* ($C_{24}H_{32}O_3S$) C, H.

γ-Mercapto-3-oxoandrost-4-ene-Δ^{17,γ}-crotonic Acid γ-Lactone (5).—When 875 mg of thiolactone **4d** was treated with Al(O-*i*-Pr)$_3$ and Me_2CO following the procedure described above, 560 mg of cream-colored solid was obtained which upon recrystallization (Me_2CO) gave 392 mg (45%) of thiolactone **5**, mp 215–225°. Further recrystallization (Me_2CO) gave the analytical sample: mp 234–236°; $[\alpha]^{23}D$ −54.64; λ_{max}^{EtOH} 239 mμ (log ε 4.29) and 328 mμ (log ε 4.15); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 1673 (overlapping conjugated C=O groups); nmr, Table I. *Anal.* ($C_{23}H_{28}O_2S$) C, H.

Steroidal Cyclic Ethers

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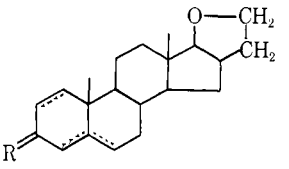
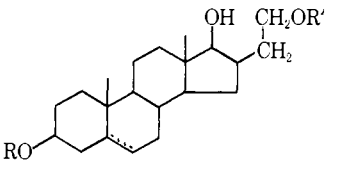
Received June 24, 1968

Several tetrahydrofuran derivatives of the androstane and estrane series were prepared by $NaBH_4$–BF_3 etherate reduction of the corresponding 17β-hydroxy-16β-acetic acid γ-lactones or by cyclization of the appropriate 16β-(2-hydroxyethyl)-17β-hydroxy steroids. The cyclic ethers were tested for estrogenic, antiestrogenic, antigonadotropic, and androgenic activities. Two of the estrane derivatives exhibited weak estrogenic properties while the remaining compounds were biologically inactive.

The observed antiestrogenic activites of a cyclic ether derivative of 19-nortestosterone, 4′,5′-dihydrospiro[estr-4-ene-17,2′(3′H)-furan]-3-one,[1] and a number of closely related compounds,[2] as well as the reported effectiveness of some of these substances as aldosterone antagonists,[3] suggested a study of the biological properties of a series of androstanes and estranes having a tetrahydrofuran structure fused to the D ring. The preparation of these compounds from a number of lactones or their precursors in the androstane[4] and estrane[5] series is reported.

$NaBH_4$–BF_3 etherate reduction[6] of 3β,17β-dihydroxy-5α-androstane-16β-acetic acid γ-lactone (**1**)[4] yielded 17β,2′-epoxy-16β-ethyl-5α-androstan-3β-ol (**2a**) in 34% yield together with a 46% yield of 16β-(2-hydroxyethyl)-5α-androstane-3β,17β-diol (**3a**). The major reduction product **3a** was allowed to react with *p*-toluenesulfonyl chloride in pyridine to give a mixture containing the mono- and the di-*p*-toluenesulfonates **3b** and **3c**. Treatment of the crude *p*-toluenesulfonate mixture with KO-*t*-Bu in *t*-BuOH essentially following the cyclization procedure of Brown,[2] led to the formation of the 3β-hydroxy ether **2a** and the *p*-toluenesulfonate **2b**. The latter (**2b**) was cleaved to **2a** with sodium in liquid ammonia–ammonium chloride.[7]





2a, R =  ; 5α-H

b, R =  ; 5α-H

4, R = O; 5α—H

5, R = O; Δ^{1,4}

8a, R =  ; Δ^5

b, R =  ; Δ^5

10, R = O; Δ^4

3a, R = R′ = H; 5α-H

b, R = H; R′ = Ts; 5α-H

c, R = R′ = Ts; 5α-H

7a, R = R′ = H; Δ^5

b, R = H; R′ = Ts; Δ^5

c, R = R′ = Ts; Δ^5

Ts = *p*-$CH_3C_6H_4SO_2$

Oxidation of **2a** in a two-phase system[8] led to the isolation of the ketone **4**, which upon dibromination followed by the elimination of the elements of HBr[9] gave the 1,4-dien-3-one **5**.

No pure reduction product could be isolated after $NaBH_4$–BF_3 etherate reduction of 3β,17β-dihydroxyandrost-5-ene-16β-acetic acid γ-lactone.[4] The desired 17β,2′-epoxy-16β-ethylandrost-5-en-3β-ol (**8a**) was obtained in the following manner. $LiAlH_4$ reduction of 3β,17β-diacetoxyandrost-5-ene-16β-acetic (**6**)[4] yielded the previously reported 16β-(2-hydroxyethyl)androst-5-ene-3β,17β-diol (**7a**).[10] The triol **7a**

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