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Thiosteroids. XXIV.[1] Synthesis of Benzo-*c*-thieno Steroid: 1-Methyl-3-acetoxy-5′-phenylthieno[4′,3′,2′-4,5,6]estra-1(10),2,5,9(11)-tetraen-17-one

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Benzo-*c*-thieno steroid, 1-methyl-3-acetoxy-5′-phenylthieno[4′,3′,2′-4,5,6]estra-1(10),2,5,9(11)-tetraen-17-one was synthesized from 5′-phenylthieno[4′,3′,2′-4,5,6]androsta-5,9(11)-diene-3,17-dione by means of dehydrogenation with DDQ followed by acid-catalyzed rearrangement.

Although benzo-*b*-thiophene and its derivatives are well known, only a few synthesis of benzo-*c*-thiophene derivatives were reported up to date.[3] Recently unsubstituted benzo-*c*-thiophene which seems to be unstable was synthesized[4] and it was found to react with maleic anhydride affording Diels–Alder type adducts.[4,5] Previously, we synthesized a number of 5′-methyl and 5′-phenylthieno[4′,3′,2′-4,5,6]-5-en-3-oxo steroids.[6,7] We wish to report now some reactions of these compounds with the aim at synthesis of a benzo-*c*-thieno steroid.

Introduction of C-1,2 double bond in 5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (I) in the usual way [with dichlorodicyanobenzoquinone (DDQ) in boiling benzene or dioxane] failed. The modified procedure by Ringold (with DDQ in dioxane in the presence of anhydrous hydrochloric acid at room temperature)[8] was also not successful and heating to 50° some 5′-methylthieno[4′,3′,2′-4,5,6]pregna-1,5-diene-3,20-dione (II) was isolated (Yield: 35%). The structure of II was supported by the nuclear magnetic resonance (NMR) spectrum which shows the AB pattern of a *cis* disubstituted olefin with a pair of doublets at 2.83 and 3.81 τ ($J_{AB}\approx$10.2 cps). Treatment of II with boron trifluoride etherate in a mixture of acetic acid and acetic anhydride did not yield the expected benzo-*c*-thieno compound. In order to characterize the methylthienoprogesterone (I) some reactions were carried out. Acylation of I with acetic anhydride and boron trifluoride etherate[9] gave 2-acetyl-5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IV) as well as its 20-enol acetate (III) in moderate yields. Oxidation of I with *t*-butyl chromate[10] afforded 3,7,20-trione (V) in 20% yield. It is interest-

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3) A. Bristrzycki and B. Brenken, *Helv. Chim. Acta*, **5**, 20 (1922); A. Bristrzycki and A. Traub, *ibid.*, **7**, 935 (1924); A. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, **61**, 2765 (1939); C.F.H. Allen and J.W. Gates, Jr., *ibid.*, **65**, 1283 (1943); O. Dann, M. Kokorudz, and R. Gropper, *Chem. Ber.*, **87**, 140 (1954); O. Dann and H. Distler, *ibid.*, **87**, 365 (1954).
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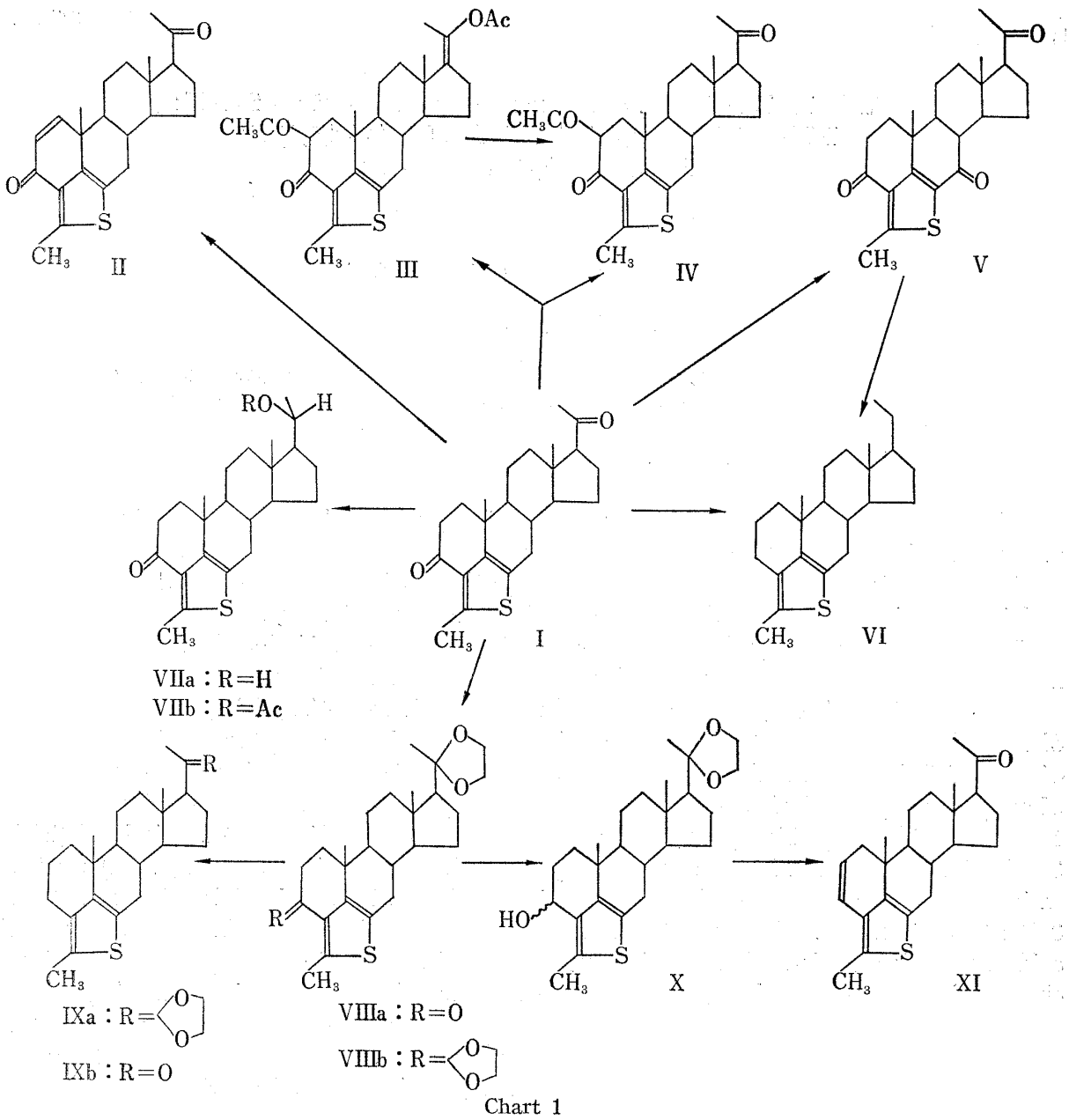

Chart 1

ing to note that in the NMR spectrum of V the peak width at half height ($W_{h/2}$) of the thiophene-methyl signal is smaller than those of the other thieno derivatives having C_7-methylene groups. This implies long range coupling through six bonds as already observed by Gronowitz.[11] Some derivatives of I were prepared as follows. Reduction of I with sodium borohydride, followed by oxidation with DDQ afforded 3-oxo-20β-ol (VIIa), 20β-configuration of which was assumed based on the NMR spectrum.[12] Huang–Minlon reduction of I or V yielded the desoxopregnene derivative (VI). While the usual ketalization (with ethylene glycol and

11) It was reported that the long-range coupling constant between 2-CH_3 and 5-CH_3 in the NMR spectrum of 3-acetyl-2,5-dimethylthiophene is 0.55 cps. B. Gestoblon, S. Gronowitz, R.A. Hoffman, and B. Mathiasson, *Arkiv. für Kemi*, **23**, 517 (1965).

12)

	20α-		20β-	
	(C-18)	(C-21)	(C-18)	(C-21)
20-Hydroxyprogesterone	9.28	8.76d ($J\approx$6.0)	9.21	8.86d ($J\approx$7.0)
20-Acetoxyprogesterone	9.27	8.76d ($J\approx$7.0)	9.32	8.85d ($J\approx$6.0)

W.R. Benn, *J. Org. Chem.*, **28**, 3557 (1963); C.H. Robinson and P. Hofer, *Chem. Ind.* (London), **1966**, 377.

a trace of acid in boiling benzene) of I gave the 20-monoketal (VIIIa), the modified ketalization (distillation of a ethylene glycol solution in the presence of acid under reduced pressure)[13] yielded the 3,20-bisketal (VIIIb). Whereas the Huang–Minlon reduction of VIIIa, followed by hydrolysis with acid gave the pregnen-20-one derivative (IXb), reduction of VIIIa with sodium borohydride afforded the 3-alcohol (X), which was readily dehydrated with acid to the pregnadienone derivative (XI). In these compounds, the differences between the line widths at half height of the 18-methyl as well as the thiophene-methyl and tetramethylsilane (TMS) ($\Delta W_{h/2}$) are summarized in Table I in the same way as described by Robinson and Willia-

Table I. Line Widths at Half-Height for 18-Methyl Protons and for Thiophene-methyl Protons (cps)

Compound	3-CH	6-CH	$W_{h/2}$			$\Delta W_{h/2}$	
			(18-H)	(Thiophene-CH_3)	(TMS)	(18-H)	(Thiophene-CH_3)
VI	2	2	1.00	2.10	0.65	0.35	1.45
IXa	2	2	1.45	2.60	1.10	0.35	1.50
IXb	2	2	1.23	2.40	0.90	0.33	1.50
X	1	2	1.20	2.05	0.80	0.40	1.25
XI	1	2	1.20	2.10	0.90	0.30	1.20
I	0	2	1.00	1.35	0.60	0.40	0.75
II	0	2	1.00	1.25	0.60	0.40	0.65
VIIa	0	2	1.20	1.55	0.82	0.38	0.73
V	0	0	1.30	1.05	0.95	0.35	0.10

mson.[14] In contrast to the constant value (0.30—0.40 cps) for the 18-methyl groups the values for the thiophene–methyl groups vary according to the number of protons at C_3 and C_6.

Since we expected further stabilization of the benzo-*c*-thieno compound by additional conjugation systems, we chose 5′-phenylthieno[4′,3′,2′-4,5,6]androsta-5,9(11)-diene-3,17-dione[7]

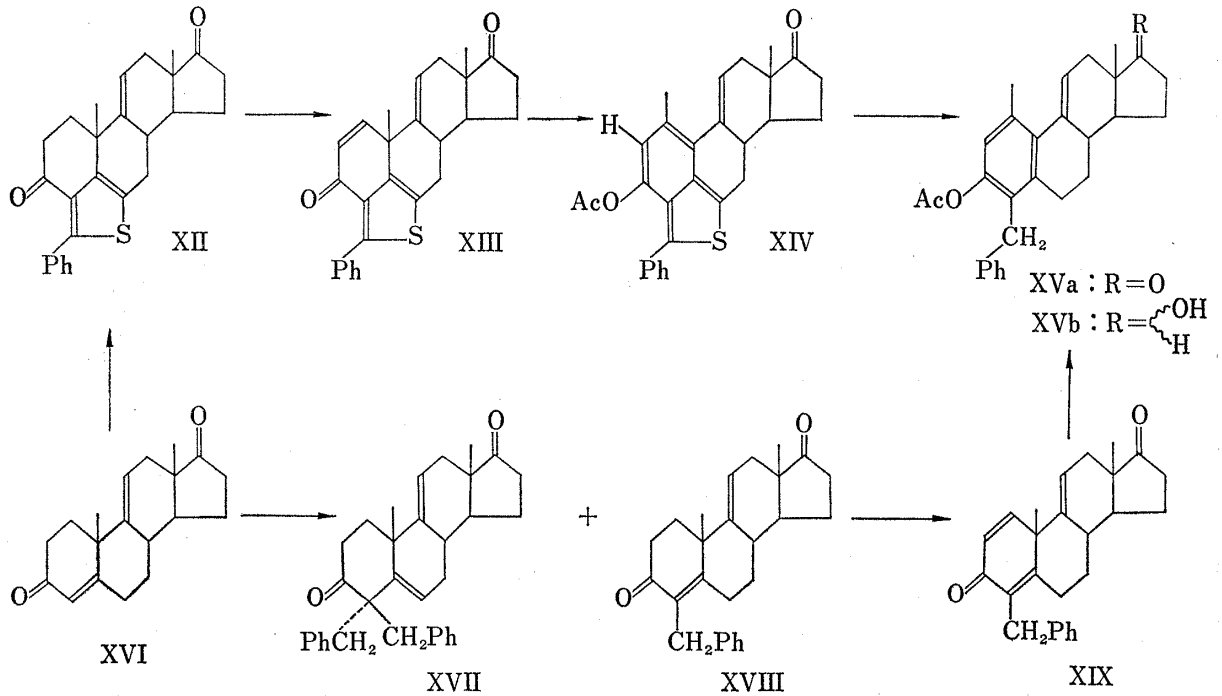

Chart 2

13) W.S. Allen, S. Bernstein, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 6116 (1956).
14) M.J.T. Robinson, *Tetrahedron Letters*, **1965**, 1685; K.L. Williamson, T. Howell, and T.A. Spencer, *J. Am. Chem. Soc.*, **88**, 325 (1966).

(XII) as substrate. Dehydrogenation of XII with DDQ in the same manner as described above afforded the trienedione derivative (XIII) in 32% yield. Brief treatment of XIII with boron trifluoride etherate in a mixture of acetic acid and acetic anhydride gave the compound (XIV), mp 164—166°, containing an enol acetoxyl group instead of the conjugated enone (infrared spectrum). Its NMR spectrum exhibits three singlets at 9.05 ($W_{h/2}\approx$1.2 cps), 8.50 ($W_{h/2}\approx$0.9 cps), and 7.58 τ ($W_{h/2}\approx$2.2 cps) due to methyl groups. The sharpest singlet was assigned to the methyl protons of the acetoxyl group shielded by the phenyl group attached to the thiophene and the broadest singlet was assigned to the C_1-methyl. One proton appeared as singlet at 3.51 τ and was assigned to the C_2–H, separated from the phenyl multiplet (5H) centered at 2.56 τ. This assignment is in accord with the structure (XIV) for the benzo-*c*-thieno compound.

Further proof was gained from the desulfurization of XIV with Raney nickel to the derivative (XVa), containing the diphenyl methane moiety, which was synthesized on an independent route. Alkylation of androsta-4,9(11)-diene-3,17-dione (XVI) with benzyl chloride in the presence of potassium tert. butoxide gave the 4-benzyl derivative (XVIII) accompanied by 4,4-dibenzylandrosta-5,9(11)-diene-3,17-dione (XVII). Dehydrogenation of the former compound with DDQ yielded 4-benzylandrosta-1,4,9(11)-triene-3,17-dione (XIX), which was treated with boron trifluoride etherate in a mixture of acetic acid and acetic anhydride to afford the diphenyl methane derivative (XVa). This compound was identified with the desulfurization product of the benzo-*c*-thieno compound by mixed melting point, comparison of the IR spectra, and thin-layer chromatography (TLC). The NMR spectrum of this compound showed the benzylic protons of the diphenyl methane structure as a singlet at 6.07 τ and the C_2-proton as a singlet at 3.14 τ.

The benzo-*c*-thieno compound (XIV) failed to give a Diels–Alder adduct with maleic anhydride.

Experimental[15]

5′-Methylthieno[4′,3′,2′-4,5,6]pregna-1,5-diene-3,17-dione (II)——Into a mixture of 3.0 g of I,[6] 2.7 g of DDQ, and 100 ml of dioxane a gentle stream of HCl was bubbled for 7 min (Gained weight of HCl: 1.43 g). The resulting mixture was warmed to 50° with stirring for 24 hr. To the solution an additional 1.4 g of DDQ was added and the mixture was further warmed to 50° with stirring for 11 hr. The appeared hydroquinone was removed by filtration and washed with benzene. The combined filtrates were washed several times with 5% NaOH and water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue (2.34 g) was chromatographed over 50 g of Florisil. The fractions eluted with pet. ether–benzene (1:1) gave an oily substance, which was soluble in ether and not studied further. The fractions (1.875 g) eluted with benzene were crystallized from ether to yield 1.083 g (35%) of the crystals, which upon recrystallization from MeOH afforded the pure sample of II, mp 161—163°, $[\alpha]_D^{24}$ −9.5±2° (c=1.061). IR ν_{max} cm^{-1}: 1692, 1646, 1572, 1502, 827. UV λ_{max} mμ (ε): 240 (12820), 283 (7740), 327 (2290). NMR (τ): (18-H) 9.26, (19-H) 8.73, (21-H) 7.83, (thiophene-Me) 7.21, (1-H, 2-H) 2.83d, 3.81d ($J_{AB}\approx$10.2). *Anal.* Calcd. for $C_{23}H_{28}O_2S$: C, 74.96; H, 7.66; S, 8.70. Found: C, 74.71; H, 7.93; S, 8.51.

Attempted Acid Catalyzed Rearrangement of II——To a cooled solution of 300 mg of II in a mixture of 10 ml of AcOH and 10 ml of Ac_2O, 0.2 ml of $BF_3\cdot OEt_2$ was added. The resulting solution was allowed to stand at room temperature with stirring for 1.5 hr, poured into ice water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 10% Na_2CO_3 and water, and dried. After removal of the solvent the residue (340 mg), which gave a tailing main spot in lower Rf than that of I on TLC, was subjected to preparative TLC, using cyclohexane–AcOEt (7:3) as developing solvent. The obtained semisolid (76 mg) was crystallized from EtOH to yield 30 mg of crystals, mp 161—163°, which were unstable and on standing decomposed gradually to give a dark brown material. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775, 1715, 1630, 1588.

15) All melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined in 1% EtOH–$CHCl_3$ with a Perkin–Elmer Polarimeter, type 141. Unless otherwise stated, IR spectra were recorded in Nujol mulls with a Koken Infrared spectrophotometer, Model DS-201B, and ultraviolet (UV) spectra in 95% EtOH on a Hitachi EPS-2 spectrophotometer. All NMR spectra were taken on $CDCl_3$ solutions with a Varian A-60 spectrometer, tetramethylsilane serving as internal standard. For preparative TLC silica gel G (Merck Co.) was used as an adsorbent.

NMR (τ): 9.31s (3H), 8.26s (3H), 7.98 (3H), 7.86s (3H), 7.45s (3H), 4.28bs (1H), 3.24. (1H). *Anal.* Found: C, 71.30; H, 7.26; S, 7.60. These data are not consistent with what would be expected for the structure of the benzo-*c*-thieno compound, and indicate probably a mixture.

2-Acetyl-5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-en-3,20-dione (III)——To a stirred mixture of 300 mg of I and 25 ml of Ac_2O, 0.7 ml of $BF_3 \cdot OEt_2$ was added. The colored mixture was allowed to stand at room temperature with stirring for 4.5 hr, poured into ice water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer separated was washed with 10% Na_2CO_3 and water. Removal of the solvent afforded 362 mg of the crude BF_3–chelate complex, which was dissolved in a solution of 100 mg of AcONa in 25 ml MeOH containing 0.3 ml of water. The resulting mixture was refluxed for 2.5 hr and concentrated to a half volume. To the mixture water was added and extracted with CH_2Cl_2. Work-up in the usual way gave 322 mg of the crude product, which showed two main spots on TLC. The Separation was submitted to preparative TLC, using cyclohexane–AcOEt (2:1) as developing solvent. The more mobile fraction gave 65 mg (17.5%) of the solid, which was recrystallized from ether–pentane to yield 36 mg of III, mp 174—176°, IR ν_{max} cm^{-1}: 1753, 1706, 1593 (broad), 1227. UV λ_{max} mμ (ε): 227 (7770), 275 (4460), 271 (4180), 340 (16400). NMR (τ): (18-H) 9.08, (19-H) 8.95, (21-H) 8.19, (Ac) 7.90 (3H) 7.87 (3H), (thiophene-Me) 7.29. *Anal.* Calcd. for $C_{27}H_{34}O_4S$: C, 72.78; H, 7.82; S, 7.77. Found: C, 72.70; H, 7.47; S, 7.73. The less mobile fraction afforded 141 mg (41.0%) of the solid, which upon recrystallization from ether–pentane yielded 103 mg of IV, mp 159—161°, IR ν_{max} cm^{-1}: 1709, 1587 (broad), 1505. UV λ_{max} mμ (ε): 229.5 (6080), 256.5 (4050), 271 (3780), 340 (16400). NMR (τ): (18-H) 9.30, (19-H) 8.94, (Ac) 7.87 (6H), (thiophene-Me) 7.28. *Anal.* Calcd. for $C_{25}H_{32}O_3S$: C, 71.33; H, 7.54; S, 7.05. Found: C, 71.33; H, 7.54; S, 7.42. Treatment of 36 mg of III with 10% Na_2CO_3-aq. MeOH afforded 13 mg of crystals, mp 160—162°, identical with IV by mixed mp, the IR spectrum, and TLC.

5′-Methylthieno[4′,3′,2′-4,5,6]pregn-5-ene-3,7,20-trione (V)——To a boiled solution of 2.50 g of I in 40 ml of CCl_4 a mixture of 15 ml of AcOH, 10 ml of Ac_2O, and 40 ml of *t*-butyl chromate–CCl_4 solution was added dropwise with stirring for 2 hr and the resulting mixture was refluxed with stirring for 19 hr. The excess reagent was decomposed by addition of a saturated solution of oxalic acid to the cooled mixture. The organic layer separated was washed successively with water, 10% Na_2CO_3 and water, and dried. After removal of the solvent, the oily product (2.0 g) was chromatographed over 200 g of silica gel-H, using cyclohexane–AcOEt (2:1) as developing solvent and a fraction-collector apparatus. The first fractions eluted with 360 ml of the solvent afforded 100 mg of the starting material (I). The second fractions eluted with 280 ml of the solvent gave 50 mg of an impure mixture. The third fractions eluted with 440 ml of the solvent yielded 756 mgof the solid, which was recrystallized from MeOH affording 535 mg (20.6%) of V, mp 182—183°, $[\alpha]_D^{22}$ $-12.1 \pm 2°$ (c=1.007). IR ν_{max} cm^{-1}: 1708, 1698, 1675, 1545, $\nu_{max}^{CCl_4}$ cm^{-1}: 1710, 1673, 1540. UV λ_{max} mμ (ε): 254(28400), 288 (9720). NMR (τ): (18-H) 9.25; (19-H) 8.65, (21-H) 7.86, (thiophene-Me) 7.18. *Anal.* Calcd. for $C_{23}H_{28}O_3S$: C, 71.84; H, 7.36; S, 8.34. Found: C, 71.92; H, 7.39; S, 8.58. Further elution with 220 ml of the solvent gave 27 mg of an impure mixture.

5′-Methylthieno[4′,3′,2′-4,5,6]pregn-5-ene (VI)——a) A mixture of 740 mg of I, 600 mg of KOH, 3 ml of 80% NH_2–NH_2–H_2O, and 14 ml of triethylene glycol was treated in a similar manner as described later. The oily product (650 mg), dissolved in pet. ether, was chromatographed over 20 g of standardized Al_2O_3. The fractions eluted with pet. ether were recrystallized from acetone–MeOH giving 457 mg (66.9%) of VI, mp 100—101°, $[\alpha]_D^{26.5}$ $+14.5 \pm 2°$ (c=1.029), UV λ_{max} mμ (ε): 246 (8470). *Anal.* Calcd. for $C_{23}H_{34}S$: C, 80.64; H, 10.00; S, 9.36. Found: C, 80.74; H, 9.85; S, 9.06.

b) Trione (V) (78 mg) was added to a mixture of 130 mg of KOH, 0.5 ml of 80% NH_2–NH_2–H_2O, and 5 ml of triethylene glycol. The resulting mixture was treated as described later. Chromatography of the oily product (70 mg) over 1.4 g of Al_2O_3 afforded 40 mg of the solid, which was recrystallized from MeOH to give 25 mg of crystals, mp 99—100°, identical with a sample of VI by mixed mp determination and the IR comparison.

20β-Hydroxy-5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-en-3-one (VIIa)——To a cooled suspension of 3.00 g of I in 90 ml of MeOH 600 mg of $NaBH_4$ was added portionwise with stirring. The mixture was agitated at room temperature for 1 hr, poured into water, and the mixture was extracted with CH_2Cl_2. After work-up in the usual way the product (*ca.* 3.0 g) was dissolved in 240 ml of dioxane and 2.4 g of DDQ was added. The resulting mixture was stirred at room temperature for 2 hr. The appeared hydroquinone was filtered off, and washed with benzene. The combined filtrates were several times washed with 5% NaOH and water and dried over Na_2SO_4. After removal of the solvent, the residue (2.282 g) was chromatographed over 30 g of Florisil. Fractions (1.693 g) eluted with benzene and benzene–ether (5:1) were recrystallized from acetone affording 1.232 g (41%) of VIIa, mp 170—172°, $[\alpha]_D^{23}$ $-41.1 \pm 2°$ (c=1.086). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3589, 1665, 1572, 1493. NMR (τ): (18-H) 9.17, (19-H) 8.82, (21-H) 8.85d ($J \approx 6.3$), (thiophene-Me) 7.28, (20-H) 6.22. *Anal.* Calcd.for $C_{23}H_{32}O_2S$: C, 74.15; H, 8.66; S, 8.61. Found: C, 74.43; H, 8.74; S, 8.59. Acetylation with pyridine–Ac_2O in the usual manner gave the acetate (VIIb), which was recrystallized from CH_2Cl_2–MeOH, mp 170.5—172°, $[\alpha]_D^{23}$ $-1.0 \pm 2°$ (c=1.011). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1664, 1571, 1492. NMR (τ): (18-H) 9.27, (19-H)8.83, (21-H) 8.82d ($J \approx 6.2$), (AcO) 7.97, (thiophene-Me) 7.28, (20-H) 5.10. *Anal.* Calcd. for $C_{25}H_{34}O_3S$: C, 72.42; H, 8.27; S, 7.73. Found: C, 72.37; H, 8.39; S, 7.50.

20-Ethylenedioxy-5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-en-3-one (VIIIa)——A mixture of 3.00 g of I, 6 ml of ethylene glycol, 200 mg of *p*-TsOH–H_2O, and 200 ml of dry benzene was refluxed with constant removal of water for 6 hr. After cooling the mixture was poured into iced 10% Na_2CO_3 and extracted with ether. The ethereal solution was washed with water, dried, and evaporated to dryness. The residue (3.50 g) was recrystallized from acetone to give 2.841 g (84.8%) of VIIIa, mp 142—144°, $[\alpha]_D^{22}$ −18.2±2° (c=1.101). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1668, 1565, 1490, 1050, 945. UV λ_{max} mμ (ε): 221 (12600), 269 (11500), 305 (2200). *Anal.* Calcd. for $C_{25}H_{34}O_3S$: C, 72.42; H, 8.27; S, 7.73. Found: C, 72.36; H, 8.31; S, 7.82.

3,20-Bisethylenedioxy-5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-ene (VIIIb)——A mixture of 1.00 g of I, 100 mg of *p*-TsOH–H_2O, and 50 ml of ethylene glycol was distilled at 5—6 mmHg for 3 hr, during which period 35 ml of the distillate was removed. The remained mixture, cooled, was poured into iced 10% Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and concentrated under reduced pressure. Recrystallization from MeOH afforded 989 mg (80.0%) of VIIIb, mp 165—167°, $[\alpha]_D^{22}$ +8.1±0.3° (c=1.017). IR ν_{max} cm^{-1}: 1576, 1504, 1155, 1098, 1071, 1054, 932. *Anal.* Calcd. for $C_{27}H_{38}O_4S$: C, 70.70; H, 8.35; S, 6.99. Found: C, 70.65; H, 8.24; S, 6.97.

5′-Methylthieno[4′,3′,2′-4,5,6]pregn-5-en-20-one (IXb)——A mixture of 1.634 g of VIIIa, 3 ml of 80% NH_2–NH_2–H_2O, 2.5 g of KOH and 45 ml of triethylene glycol was refluxed at 120° for 1 hr, then distilled until the inner temperature reached to 200°, and the remained mixture was heated to 200° for 2.5 hr. After cooling the mixture was added to water and extracted with ether. Work-up in the usual way afforded 1.30 g (83%) of the solid, which was recrystallized from acetone to yield 1.16 g of IXa, mp 126—128°, $[\alpha]_D^{22}$ +10.9±2° (c=1.097). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1355, 1070, 1052. UV λ_{max} mμ (ε): 246 (8500). NMR (τ): (18-H) 9.17, (19-H) 8.94, (21-H) 8.71, (thiophene-Me) 7.78, (ketal-CH_2) 6.10bs. *Anal.* Calcd. for $C_{25}H_{36}O_2S$: C, 74.95; H, 9.06; S, 8.00. Found: C, 74.90; H, 9.14; S, 8.13. The ketal (900 mg), dissolved in 30 ml of 70% AcOH, was heated on a steam-bath for 1.5 hr, cooled, and poured into water. The precipitate was filtered off, washed with water, and dried. Recrystallization from acetone gave 730 mg (92%) of IXb, mp 177—179°, $[\alpha]_D^{22}$ +74.3±2° (c=1.114). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1708. UV λ_{max} mμ (ε): 245.5 (8950). NMR (τ): (18-H) 9.32, (19-H) 8.94, (21-H) 7.88, (thiophene-Me) 7.77. *Anal.* Calcd. for $C_{23}H_{32}OS$: C, 77.47; H, 9.05; S, 8.99. Found: C, 77.29; H, 8.90; S, 8.77.

5′-Methylthieno[4′,3′,2′-4,5,6]pregna-2,5-dien-20-one (XI)——To a cooled suspension of 2.80 g of VIIIa in 200 ml of MeOH 600 mg of $NaBH_4$ was added portionwise with stirring. The mixture was agitated at room temperature for 3.5 hr, poured into ice water, and extracted with CH_2Cl_2. After work-up, the residue was twice recrystallized from acetone affording 2.210 g of X, mp 120—122°, $[\alpha]_D^{23}$ +36.5±2° (c=1.032). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3585, 1050. UV λ_{max} mμ (ε): 246 (7600). NMR (τ): (18-H) 9.17, (19-H) 8.82, (21-H) 8.70, (thiophene-Me) 7.55, (ketal-CH_2) 6.07, (3-H) 5.08. *Anal.* Calcd. for $C_{25}H_{36}O_3S$: C, 72.07; H, 8.71; S, 7.70. Found: C, 71.64; H, 8.78; S, 7.44. This compound (900 mg), dissolved in 20 ml of 70% AcOH, was heated on a steam-bath for 1 hr. The cooled mixture was poured into ice water. The precipitate was collected by filtration, washed with water, and dried. Recrystallization from acetone yielded 690 mg of XI, mp 199—201°, $[\alpha]_D^{23}$ +31.2±2° (c=1.018). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1699. UV λ_{max} mμ (ε): 230.5 inf (8600), 237 (10700), 245.5 (11700), 265.5 (15000). NMR (τ): (18-H) 9.31, (19-H) 8.98, (21-H) 7.87, (thiophene-Me) 7.67, (2-H) 4.22, (3-H) 3.58 ($J_{2H:3H}$≈9.5, $J_{2H:1H}$≈5.8, 2.9, $J_{3H:1H}$≈2.5). *Anal.* Calcd. for $C_{23}H_{30}OS$: C, 77.91; H, 8.53; S, 9.04. Found: C, 77.91; H, 8.50; S, 9.27.

5′-Phenylthieno[4′,3′,2′-4,5,6]androsta-1,5,9(11)-triene-3,17-dione (XIII)——Into a solution of 9.019 g of XII[7] and 5.30 g of DDQ in 500 ml of dioxane a gentle stream of HCl was bubbled for 5 min and the resulting mixture was warmed to 50° with stirring for 12 hr. To the solution an additional 5.3 g of DDQ was added and the mixture was further warmed to 50° with stirring for 17 hr. After working up in a similar manner as described above, the residue (4.80 g), dissolved in pet ether–benzene (1:1), was chromatographed over 200 g of Florisil. The fractions eluted with pet ether–benzene (1:1) gave a small amount of oil, which was not further studied. The fractions (3.50 g) eluted with benzene and benzene–CH_2Cl_2 (10:1) were recrystallized from CH_2Cl_2–MeOH yielding 2.856 g (31.8%) of XIII, mp 225—226°, $[\alpha]_D^{24}$ −181.9±2° (c=1.041). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738, 1660, 1599, 1566, 1505. UV λ_{max} mμ (ε): 227 (14600), 284 inf (9260), 351.5 (5650). NMR (τ): (18-H) 9.03, (19-H) 8.52, (11-H) 4.34t-d (J≈3.2, 2.0), (1-H, 2-H) 2.83d, 3.77d(J_{AB}≈10.0), (Ph–H) 2.62 m (3H), 2.33 m (2H). *Anal.* Calcd. for $C_{26}H_{24}O_2S$: C, 77.96; H, 6.04; S, 8.01. Found: C, 77.70; H, 5.93; S, 7.75.

1-Methyl-3-acetoxy-5′-phenylthieno[4′,3′,2′-4,5,6]estra(10),2,5,9(11)-tetraen-17-one (XIV)——To a solution of 800 mg of XIII in a mixture of 25 ml of AcOH and 25 ml of Ac_2O 0.5 ml of BF_3·OEt_2 was added. The resulting mixture was allowed to stand at room temperature with stirring for 1.5 hr, poured into ice water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 10% Na_2CO_3 and water, dried, and the solvent was distilled off under reduced pressure. The residue was recrystallized from CH_2Cl_2–MeOH affording 586 mg (66.3%) of XIV, mp 164—166°, $[\alpha]_D^{22}$ +344.1±2° (c= 1.018). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3056, 1766, 1743, 1600, 1535, 1497, 1374, 1195, 695. UV λ_{max} mμ (ε): 231.5 (31200), 246.5 inf (22500), 390 (11500). NMR (τ): (18-H) 9.05, (AcO) 8.50, (1-Me) 7.58, (11-H) 3.92t-d (J≈4.0, 1.0), (2-H) 3.51 s, (Ph–H) 2.65 m(5H). *Anal.* Calcd. for $C_{28}H_{26}O_3S$: C, 75.99; H, 5.92; S, 7.25. Found: C, 75.95; H 6.10; S, 7.34.

Desulfurization of the Benzo-*c*-thieno Compound (XIV)——a) A mixture of 200 mg of XIII, 2.2 g of freshly prepared W-2 Raney Ni, and 13 ml of dioxane was refluxed for 4 hr. After Ni was removed, the filtrate was evaporated to dryness *in vacuo*. The residue (171 mg) showed 3 spots on TLC. The separation was effected by preparative TLC, using cyclohexane–AcOEt (2:1) as developing solvent. The more mobile fraction (40 mg, 18%) was recrystallized from aq. MeOH affording the benzyl phenol ketone (XVa), mp 95—97°, $[\alpha]_D^{22}$ +173.7±2° (c=1.004). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1741, 1606, 1495, 1373. UV λ_{max} mμ (ε): 247 (12600). NMR (τ): (18-H) 8.99, (AcO) 7.82, (1-Me) 7.62, (Ph-CH_2-Ph) 6.07s (2H), (11-H) 4.32t-d, (2-H) 3.14s, (Ph-H) 2.84m (5H). *Anal.* Calcd. for $C_{28}H_{30}O_3$: C, 81.13; H, 7.30. Found: C, 81.30; H, 7.52. The less mobile fraction (54 mg) exhibited the absorption band due to a hydroxyl group in the IR spectrum and Jones oxidation afforded XVa. The least mobile fraction (28 mg) was again oxidized to XVa.

b) A mixture of 400 mg of XIV, 4.7 g of Raney Ni, and 25 ml of dioxane was treated as described above. The crude product (378 mg) was oxidized with Jones reagent in acetone to give 283 mg of the solid, which was purified by preparative TLC to afford 165 mg (43.3%) of XVa.

Benzylation of Androsta-4,9(11)-diene-3,17-dione (XVI)——To a boiled solution of 5.6 g of XVI and 3.449 g of KOt-Bu in 80 ml of iso-PrOH a solution of 3.34 g of $PhCH_2Cl$ in 40 ml of iso-PrOH was added dropwise with stirring during 6 hr. To the cooled solution ice water was added and extracted with CH_2Cl_2. After work-up in the usual way the product was chromatographed over 200 g of neutral Al_2O_3. The fractions eluted with pet ether–benzene (2:1—1:1) gave 200 mg of an oil, which was not further studied. The fractions (1.613 g) eluted with benzene was recrystallized several times from MeOH affording 440 mg of the dibenzyl compound (XVII), mp 176—178°, $[\alpha]_D^{23}$ +30.5±2° (c=1.031). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3033, 1746, 1705, 704. NMR (τ): (18-H) 9.22, (19-H) 9.80,[16] (Ph-CH_2) 7.19d, 6.41d ($J_{AB}\approx$13.0) 7.06d, 6.84d ($J_{AB}\approx$12.0), (6-H) 4.72, (11-H) 4.22, (Ph-H) 2.86m (10H). *Anal.* Calcd. for $C_{33}H_{36}O_2$: C, 85.30; H, 7.81. Found: C, 85.34; H, 7.89. The fractions (1.540 g) eluted with benzene–ether (49:1) was recrystallized several times from aq MeOH giving 730 mg (10%) of the monobenzyl compound (XVIII), mp 116—117°, $[\alpha]_D^{22}$ +197.2±2° (c=1.089). IR ν_{max} cm^{-1}: 3014, 1746, 1673, 1633, 1603, 1497, 1023, 698. UV λ_{max} mμ (ε): 250.5 (13800). NMR (τ): (18-H) 9.12, (19-H) 8.63, (Ph-CH_2) 6.27s (2H), (11-H) 4.45, (Ph-H) 2.86m (5H). *Anal.* Calcd. for $C_{26}H_{33}O_2$: C, 83.38; H, 8.07. Found: C, 83.45; H, 8.14.

4-Benzylandrosta-1,4,9(11)-triene-3,17-dione (XIX)——A mixture of 446 mg of XVIII, 400 mg of DDQ, and 35 ml of dioxane was heated to 120° for 25 hr. The appeared hydroquinone was removed by filtration and washed with benzene. The combined filtrates were washed several times with 5% NaOH and water, dried, and evaporated. The residue, dissolved in benzene, was passed through a column of Al_2O_3 (5 g) and the column was washed with benzene. The combined benzene solutions were evaporated to dryness *in vacuo*. Recrystallization of the residue (303 mg) from MeOH afforded 215 mg (48%) of XIX, mp 172—174°, $[\alpha]_D^{22}$ +143.8±2° (c=1.080). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3011, 1747, 1671, 1638, 1608, 1498, 698. UV λ_{max} mμ (ε): 239 (12600), 271inf (6000). NMR (τ): (18-H) 9.10, (19-H) 8.56, (Ph-CH_2) 6.16s (2H), (11-H) 4.44, (1-H, 2-H) 2.82d, 3.67d ($J_{AB}\approx$10.5), (Ph-H) 2.84m (5H). *Anal.* Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.78; H, 7.60.

1-Methyl-3-acetoxy-4-benzylestra-1,3,5(10),9(11)-tetraen-17-one (XVa)——To a solution of 135 mg of XIX in a mixture of 8 ml of AcOH and 8 ml of Ac_2O 0.01 ml of $BF_3\cdot OEt_2$ was added. The resulting mixture was allowed to stand at room temperature with stirring for 1 hr, poured into iced water, and the mixture was extracted with ether. After work-up in the usual way, the product was purified by preparative TLC, using cyclohexane–AcOEt (2:1) as developing solvent. The main fraction was recrystallized from pentane yielding 99 mg of XVa, identity of which with the desulfurization product described before was confirmed by mixed mp and comparison of the IR spectrum.

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16) The shift to the high field is probably attributable to the shielding effect due to a benzene ring of the 4β-benzyl group. It was also reported that the 19-methyl signal appeared at 9.87 τ in the NMR spectrum of 4α-methyl-4β-benzylcholest-5-en-3-one: J.T. Pinhey and K. Schaffner, *Chem. Commun.*, **1965**, 579.