Steroidal Thiazenones and Related Compounds[1]

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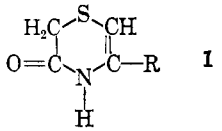
Steroids with a thiazenone ring fused to the 2,3-positions have been prepared. Also, the reaction of methyl mercaptoacetate with a 2α-bromo-3-ketosteroid has led to a series of 2-mercapto-3-oxygenated derivatives, some of which were cyclized. Evidence for the configuration of the mercapto substituent at C-2 is presented.

Androstano[3,2-*e*]thiazenones have been prepared by the condensation of mercaptoacetamide with 2α-bromo-3-ketoandrostanes. Since this new class of steroidal heterocycles contains a heterocyclic ring fused to carbons 2 and 3 of the steroid nucleus, it is similar to the androstano[3,2-*c*]pyrazoles[2] and androstano[2,3-*d*]isoxazoles[3] which were previously prepared in these laboratories and found to possess a favorable ratio of anabolic to androgenic activity.

Sokol and Ritter[4] observed that simple α-halomethyl ketones reacted with mercaptoacetamide to form products which were later characterized by deStevens, *et al.*,[5] as having the 1,4-thiaz-5-en-3-one structure (**1**).



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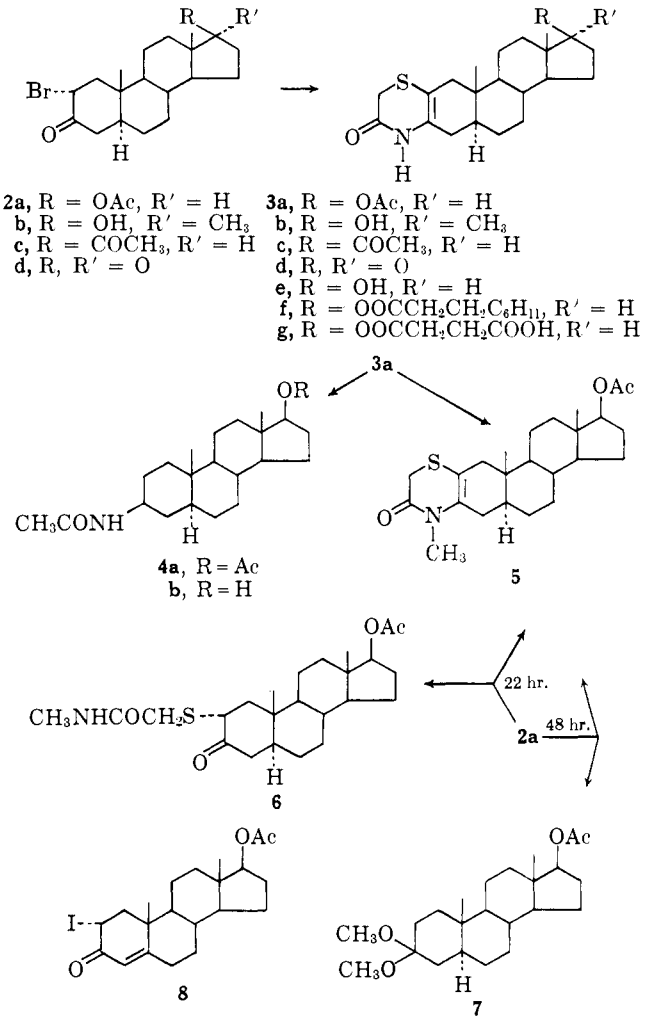
In this laboratory, the condensation of mercaptoacetamide with steroidal 2α-bromo 3-ketones (**2a–d** and **12**) afforded in each case the corresponding thiazenone (**3a–d** and **13**). The reaction was carried out in either methanol or acetonitrile at reflux temperature, usually under nitrogen with a reaction period of 24–36 hr. Curiously, in the reaction between **2a** and mercaptoacetamide using methanol as the solvent, potentiometric titration of aliquots of the reaction mixture after 1.25, 3.5, and 48 hr. revealed that no acidity developed during the course of the reaction. Addition of 2 molar equiv. of collidine to the reaction mixture resulted in only a slight improvement in yield of the thiazenone. The 17β-acetoxyl group in **3a** could be hydrolyzed by aqueous methanolic potassium carbonate to give **3e** without attack on the thiazenone ring. Compound **3e** was converted to its 17β-cyclohexylpropionate (**3f**) and 17β-hemisuccinate (**3g**) esters.

The ultraviolet spectrum of each of the thiazenones showed an expected[5] absorption maximum at 295–299 mμ (ε 2300–2600) and a shoulder at 230–232 mμ (ε 3800–4300). One derivative (**3d**) was so insoluble in most solvents that its ultraviolet spectrum had to be measured in dimethylformamide, thereby permitting detection of only the absorption maximum at 295 mμ (ε 2270).



There has been no unequivocal evidence that thiazenones were formed through replacement of halogen by sulfur and of carbonyl oxygen by nitrogen in α-haloketones, rather than the reverse attachment.[5] We have established that nitrogen in the thiazenone ring is indeed attached to the steroid nucleus at C-3. Thus, desulfurization of **3a** with Raney nickel[6] gave the saturated acetylamino derivative **4a**, which has been described previously.[7] Selective hydrolysis of **4a** by

(1) Steroidal Heterocycles IX. For preceding paper, see D. K. Phillips and A. J. Mason, *J. Org. Chem.*, **28**, 2886 (1963).

(2) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(3) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(4) H. Sokol and J. J. Ritter, *J. Am. Chem. Soc.*, **70**, 3517 (1948).

(5) G. deStevens, A. Halamandaris, and L. Dorfman, *ibid.*, **80**, 5198 (1958).

(6) C. Djerassi, N. Crossley, and M. A. Kielczewski [*J. Org. Chem.*, **27**, 1112 (1962)] reported that the production of saturated *vs.* unsaturated enamine was dependent upon the age of the Raney nickel. We have no data on the age of the Raney nickel used in our desulfurization reaction.

(7) S. A. Oletta, Belgian Patent 596,561 (November 15, 1960).

warming it briefly with aqueous alcoholic hydrochloric acid gave the 17β-hydroxy derivative (**4b**). Additional evidence supporting the assigned structure for the thiazenones was obtained when treatment of the 2α-carbomethoxymethylmercapto 3-ketone (**15**) with ammonia afforded the thiazenone **3a** (see below).

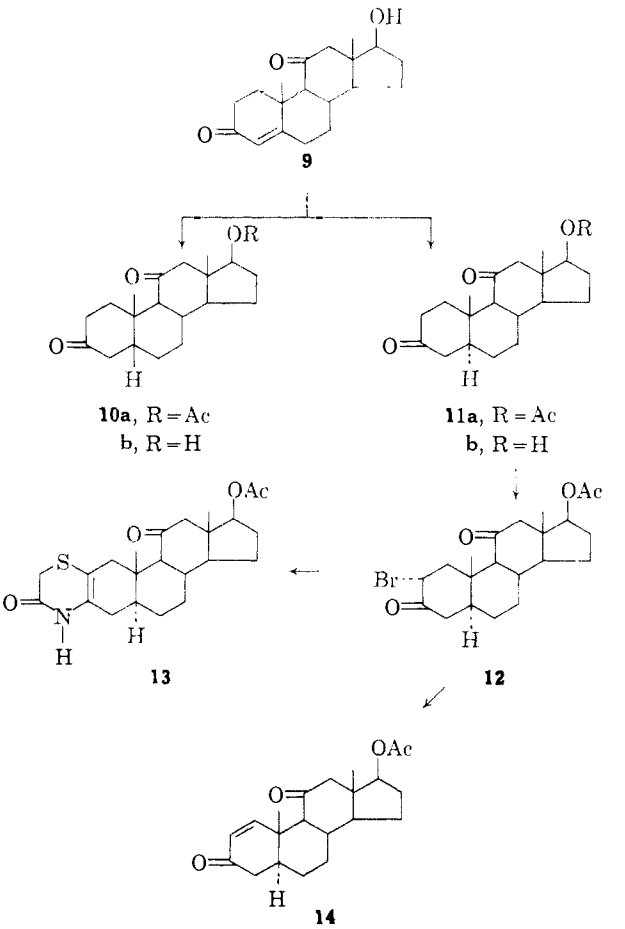
Direct methylation of the thiazenone ring in **3a** with sodium hydride and methyl iodide[8] afforded the N-methylated product (**5**) in 6% yield. The same compound could be prepared by treatment of bromo ketone **2a** with N-methylmercaptoacetamide in acetonitrile. When the latter reaction mixture was refluxed for 22 hr., **5** was obtained in 14% yield and a 24% yield of the open-chain product (**6**) was also isolated. When the reaction was repeated with a 48-hr. reflux period, a better yield (33%) of **5** was obtained, but the only other crystalline compound isolated was a dimethyl ketal (**7**, 10% yield) in which the substituent at C-2 had been removed reductively. The methanol needed for ketal formation must have been present in the crude N-methylmercaptoacetamide (see Experimental section). Acidic hydrolysis of dimethyl ketal **7** afforded 17β-hydroxy-5α-androstan-3-one. A sample of **7** was prepared from 17β-acetoxy-5α-androstan-3-one for comparison with that obtained above.

An attempt to form a 4-androsteno[3,2-*e*]thiazenone by condensation of 2α-iodo-17β-acetoxyandrost-4-en-3-one (**8**)[8] with mercaptoacetamide was not successful. Only starting material (58%) could be recovered from the reaction.

An 11-oxoandrostano[3,2-*e*]thiazenone (**13**) was synthesized in five steps, starting with adrenosterone.[9] Reduction of adrenosterone with sodium borohydride in aqueous ethanol[10] afforded a 75% yield of the 17β-hydroxyl derivative (**9**). Catalytic hydrogenation of **9** followed by acetylation of the crude product and careful chromatography afforded two compounds epimeric at C-5. Hydrolysis of the epimer melting at 197–199.5° (21% yield) to the known 17β-alcohol (**10b**)[11] established its identity as the A/B-*cis* compound (**10a**). The epimer melting at 158–160° (30% yield) was, therefore, the A/B-*trans* compound (**11a**). This was hydrolyzed to its 17β-hydroxyl derivative (**11b**). Bromination of **11a** afforded its 2α-bromo derivative (**12**), which was condensed with mercaptoacetamide to give the thiazenone **13**.

Dehydrobromination of **12** to the 1,2-unsaturated ketone (**14**) was accomplished in 94% yield by treatment with lithium bromide and lithium carbonate in dimethylformamide.

One oxygen-containing analog (**16**) of the thiazenone (**3a**) and several compounds related to it were synthesized. Methyl mercaptoacetate was condensed with bromo ketone **2a** and the product (**15**) was cyclized with *p*-toluenesulfonic acid to a dihydro oxathiinone (**16**). An attempt to cyclize **15** with acetyl chloride and acetic anhydride resulted in the formation of an enol acetate (**17**). Treatment of **15** with ammonia in either methanol or acetonitrile gave the same thiazenone (**3a**) which had been prepared from **2a** and mercaptoacetamide.



Reduction of keto ester **15** with lithium tri-*t*-butoxyaluminohydride followed by chromatography resulted in the isolation of two crystalline products (**18** and **19**). The cyclized product (**18**) could be obtained by deliberate acid-catalyzed cyclization of **19**.

The mercapto group at C-2 was shown to have the α-configuration in this series of compounds. Opening of the enol lactone ring of **16** by alkaline hydrolysis gave a keto acid (**20**) which, by its mode of formation, can be concluded to have the more stable 2α-configuration for its carboxymethylmercapto group. Keto acid **20** was also obtained by alkaline hydrolysis of keto ester **15**. Reduction of keto acid **20** with lithium tri-*t*-butoxyaluminohydride afforded 2α-carboxymethylmercapto-5α-androstane-3β,17β-diol (**21**). The same product was obtained by saponification of hydroxy ester **19**. Since keto ester **15** was reduced to hydroxy ester **19** under conditions[12] which would not be expected to epimerize an axial substituent α to a ketone, and since hydroxy ester **19** was hydrolyzed to a compound (**21**) in which the α-configuration at C-2 had been demonstrated, the substituent at C-2 in keto ester **15** and in the compounds derived from it must occupy the more stable equatorial (α) position. Assignment of the α-configuration to the C-2 substituent in keto amide **6** was based on the fact that it was formed in a manner analogous to that of keto ester **15**.

Biological Results.—The myotrophic and androgenic

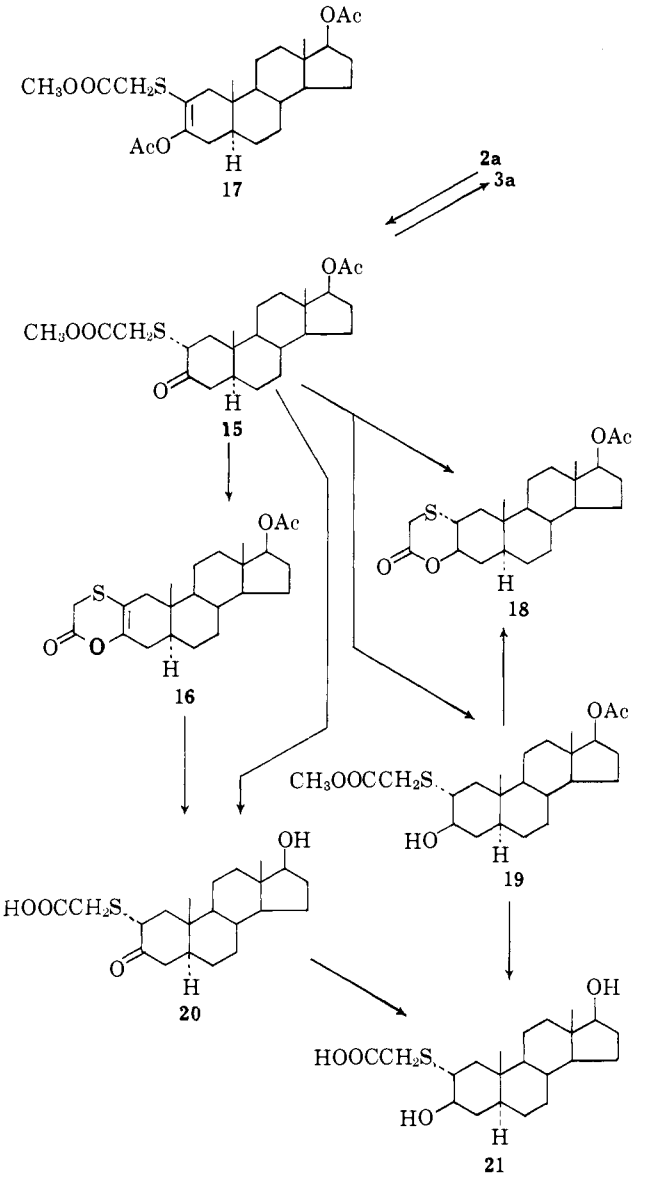
(8) B. Berkoz, A. D. Cross, M. E. Adams, H. Carpio, and A. Bowers, *J. Org. Chem.*, **28**, 1976 (1963).

(9) Prepared from cortisone by the method of C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(10) A modification of the procedure of J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(11) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 266 (1953).

(12) J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).



activities of **3a, 3b, 3e,** and **3g** were determined by a modification of the method of Hershberger, *et al.*[13] Immature male rats of the Sprague–Dawley strain, 22 days of age (41–44 g.), were castrated and maintained on laboratory chow and tap water *ad libitum* in air conditioned quarters. Each compound was administered subcutaneously daily except Sunday for 9 days, starting 7 days after castration. The animals were autopsied on the 17th post-castration day, 24 hr. after the last medication. The levator ani muscle and ventral prostate were excised, blotted, and weighed on a microtorsion balance. The myotrophic and androgenic activities relative to testosterone propionate are presented in Table I, together with indices of separation.

TABLE I

MYOTROPHIC AND ANDROGENIC POTENCIES RELATIVE TO TESTOSTERONE PROPIONATE

Compound	Myotrophic	Androgenic	Separation index[a]
3e	1/4	1/32	8
3a	1/8	1/32	4
3b	1/8	1/32	4
3g	1/8	1/32	4

[a] Separation index is the ratio of the relative myotrophic to relative androgenic potencies with testosterone propionate as the reference standard.

Experimental[14]

17β-Acetoxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3a).—A solution of 22.3 g. (0.054 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one (**2a**),[15] 7.4 g. (0.081 mole) of mercaptoacetamide,[3] and 13.1 g. (0.108 mole) of γ-collidine in 500 ml. of acetonitrile was refluxed under nitrogen for 36 hr. About 300 ml. of solvent was removed *in vacuo* at <45°, and the mixture was cooled in ice. The precipitate was collected, washed with water and methanol, and then dried to give 18.0 g. (82%) of the title compound; m.p. 333–336° dec. (evac. cap., uncorr.); $[\alpha]^{25}D$ −20.0°; λ_{max} 230 mμ (ε 4100) and 299 (2600). The melting point was not raised by further recrystallization from acetonitrile.

Anal. Calcd. for $C_{23}H_{33}NO_3S$: C, 68.44; H, 8.25; S, 7.95. Found: C, 68.5; H, 8.0; S, 7.8.

17β-Hydroxy-17α-methyl-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3b).—Mercaptoacetamide was prepared by dissolving 4.8 g. (0.04 mole) of methyl mercaptoacetate in 35 ml. of 15% ethanolic ammonia, allowing the solution to stand overnight in a nitrogen atmosphere, and concentrating to a residue by warming *in vacuo*.

To the residue of mercaptoacetamide was added a solution of 7.85 g. (0.021 mole) of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (**2b**)[16] in 300 ml. of methanol. This solution was refluxed for 3 hr., concentrated to 35 ml. by warming *in vacuo*, cooled, and filtered to collect a crop of crystalline product. Concentration of the filtrate to 15 ml. afforded a second crop. Three recrystallizations of the total solid from methanol afforded 1.87 g. (24%) of title compound; $[\alpha]^{25}D$ −25.5°, λ_{max} 232 mμ (ε 3800) and 298 (2400), which softened at 285° and melted at 297–310°. The third recrystallization produced no change in melting point. This product melted at 298–308° with intumescence in an evacuated Pyrex capillary tube.

Anal. Calcd. for $C_{21}H_{31}NO_2S$: C, 70.41; H, 9.65; S, 8.54. Found: C, 70.4; H, 9.8; S, 8.8.

20-Oxo-5α-pregnano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3c).—A mixture of 3.95 g. (0.0100 mole) of 2α-bromo-5α-pregnane-3,20-dione (**2c**),[17] 1.82 g. (0.0046 mole) of mercaptoacetamide, and 140 ml. of methanol was refluxed under a nitrogen atmosphere for 22.5 hr. At no time was the mixture homogeneous. It was cooled and filtered to give 1.2 g. (67%) of **3c**, m.p. 288–292° dec. (uncorr.). A single recrystallization from acetone–methylene dichloride afforded the analytical sample; m.p. 285.5–289° dec.; $[\alpha]^{25}D$ +58.6°; λ_{max} 230 mμ (ε 3900) and 299 (2400).

Anal. Calcd. for $C_{23}H_{33}NO_2S$: C, 71.32; H, 8.53; S, 8.28. Found: C, 71.0; H, 8.4; S, 8.1.

17-Oxo-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3d).—A solution of 2.0 g. (5.5 mmoles) of 2α-bromo-5α-androstane-3,17-dione (**2d**),[15] 0.57 g. (6.3 mmoles) of mercaptoacetamide, 1.3 g. (11 mmoles) of γ-collidine, and 50 ml. of acetonitrile was refluxed for 36 hr. under nitrogen. The precipitate was collected, washed with acetonitrile, water, and acetone, and dried to give 1.2 g. (61%) of **3d**, m.p. 378–380° dec. (evac. cap., uncorr.). The analytical sample, which was prepared by recrystallization from dimethylformamide, melted at 387–390° dec. (evac. cap., uncorr.); $[\alpha]^{25}D$ +26.0° (1% in pyridine); λ_{max}^{DMF} 295 mμ (ε 2270).

Anal. Calcd. for $C_{21}H_{39}NO_2S$: C, 70.15; H, 8.13; S, 8.92. Found: C, 69.8; H, 8.0; S, 8.8.

17β-Hydroxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3e).—To 9.0 g. (22 mmoles) of 17β-acetoxy-5α-androstano-[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (**3a**) in 1500 ml. of methanol was added 9.0 g. of potassium bicarbonate in 50 ml. of water and the resulting solution refluxed for 24 hr. The solution was concentrated until the product began to crystallize, the mixture was

(13) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

(14) Melting points are corrected unless otherwise stated. Specific rotations were measured on 1% solutions in chloroform except as noted. Ultraviolet spectra were measured in 95% ethanol with the one exception noted where dimethylformamide (DMF) was used. We are grateful to Dr. F. C. Nachod and staff for the spectral data and to Mr. K. D. Fleischer and staff for analytical services.

(15) C. Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

(16) Syntex S. A., British Patent 750,834 (June 20, 1956).

(17) M. Rubin, H. Wishinsky, and F. Bompard, *J. Am. Chem. Soc.*, **73**, 2338 (1951).

cooled, and the precipitate collected to give 7.2 g. (90%) of **3e**, which melted at 264–267° dec. (evac. cap.). Two recrystallizations from methanol afforded the analytical sample; m.p. 267–271° dec. (evac. cap.); $[\alpha]^{25}D$ −7.8; λ_{max} 230 mμ (ε 3900) and 298 (2400).

Anal. Calcd. for $C_{21}H_{31}NO_2S$: C, 69.76; H, 8.64; S, 8.87. Found: C, 69.7; H, 8.9; S, 8.7.

17β-(3-Cyclohexylpropionoxy)-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3f).—A mixture of 3.7 g. (0.010 mole) of 17β-hydroxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (**3e**), 11 g. (0.02 mole) of 3-cyclohexylpropionic anhydride, and 50 ml. of pyridine was heated at 100° for 6 hr., cooled, and poured into 1.5 l. of water. The solid which precipitated was collected and dissolved in chloroform. This solution was washed with saturated sodium bicarbonate solution, dried over Drierite, and concentrated to a residue. Chromatography of the residue on 150 g. of silica gel using a mixture of 15% methylene dichloride, 30% ether, and 55% pentane for elution separated the desired ester from oily impurities and starting material. The solid ester was recrystallized once from methylene dichloride–ethyl acetate with charcoal treatment and twice more from methylene dichloride–methanol to give 1.04 g. (20%) of **3f**; m.p. 268–269° dec.; $[\alpha]^{25}D$ −8.8°; λ_{max} 230 mμ (ε 4300) and 298 (2300).

Anal. Calcd. for $C_{30}H_{45}NO_3S$: C, 72.10; H, 9.08; S, 6.42. Found: C, 71.8; H, 8.8; S, 6.6.

17β-Hydroxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one 17-Hemisuccinate (3g).—A solution of 3.0 g. (8.3 mmoles) of 17β-hydroxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (**3e**) and 15 g. of succinic anhydride in 60 ml. of pyridine was heated on a steam bath for 4 hr. The black solution was cooled and poured into 400 ml. of water. The precipitate was collected (3.4 g.) and recrystallized from acetone–hexane to give 2.0 g. (52%) of **3g**, m.p. 271–272° (evac. cap.). One recrystallization from acetone afforded the analytical sample with the melting point unchanged; $[\alpha]^{25}D$ −32.8° (1% in pyridine); λ_{max} 230 mμ (ε 4100) and 298 (2600).

Anal. Calcd. for $C_{25}H_{35}NO_5S$: C, 65.04; H, 7.64; S, 6.95. Found: C, 64.8; H, 7.3; S, 7.2.

Desulfurization of 17β-Acetoxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one Acetate (3a).—A mixture of 3.0 g. (0.0074 mole) of **3a**, 3 teaspoonfuls of Raney nickel,[6] and 150 ml. of absolute ethanol was refluxed for 7 hr., cooled, and filtered. The filtrate was concentrated to a residue which was recrystallized from ethyl acetate to give 1.17 g. (42%) of **3β-acetylamino-5α-androstan-17β-ol acetate (4a)**, m.p. 272–275°. Two further recrystallizations raised the melting point to 277–279°. The analytical sample, thus purified, showed $[\alpha]^{25}D$ −2.1° (1% in EtOH).

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.37. Found: C, 73.4; H, 10.0; N, 3.7.

This product showed no depression in melting point upon admixture with an authentic sample,[7] m.p. 277–279°, and the infrared spectra of the two materials were identical.

3β-Acetylamino-5α-androstan-17β-ol (4b).—A boiling mixture of 1.46 g. (0.0039 mole) of 3β-acetylamino-5α-androstan-17β-ol acetate (**4a**) and 18 ml. of absolute ethanol was treated with 36 ml. of 25% aqueous hydrochloric acid and the mixture was refluxed for 0.5 hr. The solid initially present dissolved and a precipitate then formed. The mixture was cooled and filtered and the solid thus collected was dissolved in 15 ml. of hot methanol. Addition of 1.5 ml. of water and cooling afforded 1.13 g. (87%) of colorless plates, m.p. 236–238°, $[\alpha]^{25}D$ −3.3° (1% in EtOH). This sample was dried at 155° (10 mm.) for 5 hr.

Anal. Calcd. for $C_{21}H_{35}NO_2$: C, 75.62; H, 10.58; N, 4.20. Found: C, 75.6; H, 10.8; N, 4.1.

17β-Acetoxy-5α-androstano[3,2-*e*]-4′-methyl-1′,4′-thiaz-5′-en-3′-one (5) by Direct Methylation of 17β-Acetoxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3a).—A solution of 1.0 g. (2.5 mmoles) of **3a** in 100 ml. of dry benzene was treated with 119 mg. (2.5 mmoles) of 50% sodium hydride in mineral oil and the mixture refluxed for 4 hr. under nitrogen. It was cooled to room temperature, 2 ml. of methyl iodide was added, and the resulting mixture refluxed overnight. The precipitate which formed during the reaction was removed by filtration through Filtercel and the filtrate concentrated to dryness. The residual oil was triturated with ether and the crystalline solid which formed was collected and dried to give 0.1 g. of crude starting material, m.p. 277–310° (evac. cap.). Concentration of the filtrate afforded a crude crystalline residue which was taken up in a 2:3 benzene–pentane mixture and chromatographed on 30 g. of silica gel. Elution with a 1:3 ether–benzene mixture afforded, after recrystallization from acetone–hexane, 65 mg. of **5**, m.p. 214–217°. Four recrystallizations from acetonitrile gave a sample of m.p. 223–227°; its infrared spectrum was identical with that of the sample prepared from the bromoketone **2a** (see below) and the mixture melting point of the two substances was not depressed.

17β-Acetoxy-5α-androstano[3,2-*e*]-4′-methyl-1′,4′-thiaz-5′-en-3′-one (5) and 2α-N-Methylcarbamylmethylmercapto-17β-acetoxy-5α-androstan-3-one (6).—Methylamine was bubbled into 350 ml. of methanol until 41.5 g. had been absorbed (35 min.). After 25 g. of methyl mercaptoacetate was added, the solution was kept overnight at room temperature and then concentrated to dryness by warming *in vacuo*. A 4.5-g. (0.043 mole) portion of this crude N-methylmercaptoacetamide was added to 10.0 g. (0.024 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one (**2a**) and 5 ml. of γ-collidine in 350 ml. of acetonitrile and the resulting solution was refluxed for 22 hr. under nitrogen. The solvent was removed by warming *in vacuo* and the residue was partitioned between water and ether. The layers were separated and the organic layer was washed with 2 *N* hydrochloric acid, water, and saturated salt solution and dried over anhydrous magnesium sulfate, then evaporated to dryness. Recrystallization of the crude residue from acetone–hexane afforded 4.5 g. of ketoamide **6**, m.p. 153–159°. Three further recrystallizations from methanol gave 2.55 g. (24%) of purified material, m.p. 164–165.5°, $[\alpha]^{25}D$ −12.7°.

Anal. Calcd. for $C_{24}H_{37}NO_4S$: C, 66.17; H, 8.56; S, 7.36. Found: C, 66.3; H, 8.6; S, 7.5.

Concentration and cooling of the mother liquor from the first recrystallization above afforded 0.85 g. of the N-methylthiazenone **5**, m.p. 220–223°. A sample which was recrystallized from acetonitrile melted at 223.5–228°; $[\alpha]^{25}D$ −91.9°; λ_{max} 228 mμ (ε 4540) and 291 (2370).

Anal. Calcd. for $C_{24}H_{35}NO_3S$: C, 69.02; H, 8.45; S, 7.68. Found: C, 69.3; H, 8.4; S, 7.7.

All mother liquors were combined and refluxed with 10 ml. of triethylamine in 350 ml. of acetonitrile for 3 days. Concentration on a steam bath *in vacuo* and crystallization of the residue from acetonitrile gave an additional 0.32 g. of **5**, m.p. 222–224°. The mother liquor afforded *ca.* 6 g. of a dark brown oil which was chromatographed on silica gel. Elution with 1:2:7 methylene dichloride–ether–pentane gave, after recrystallization from methanol, 0.80 g. of impure **6**, m.p. 153–157°. Elution with 1:3:6 methylene dichloride–ether–pentane afforded, after recrystallization from acetonitrile, 0.45 g. of the N-methylthiazenone **5**, m.p. 221–225° (14% total yield).

Extension of the reflux period to 48 hr. and chromatography of the total product using 1:2:7 methylene dichloride–ether–pentane gave **3,3-dimethoxy-5α-androstan-17β-ol acetate (7)** as the first crystalline product eluted. Two recrystallizations from methanol afforded a 10% yield of material melting at 143–147°. The analytical sample, which was purified by recrystallization from acetone, melted at 143–146°, $[\alpha]^{25}D$ +6.4°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 72.98; H, 10.12; OMe, 16.40. Found: C, 73.2; H, 10.1; OMe, 16.6.

Further elution of the chromatographic column with the same solvent mixture afforded, after recrystallization from acetonitrile, a 33% yield of the **N-methylthiazenone 5**, m.p. 223–227°.

Hydrolysis of 3,3-Dimethoxy-5α-androstan-17β-ol Acetate (7) to 17β-Hydroxy-5α-androstan-3-one.—A solution of 150 mg. (0.38 mmole) of the dimethyl ketal **7** and 1 ml. of 4 *N* sulfuric acid in 10 ml. of methanol was kept at room temperature for 24 hr. and then poured into water. Ether was added and the organic layer was separated, washed with water and saturated salt solution, and dried over powdered magnesium sulfate. Concentration to a small volume afforded 57 mg. (54%) of 17β-hydroxy-5α-androstan-3-one, m.p. 181–183°. The mixture melting point with an authentic sample, m.p. 180.5–183°, was not depressed and the infrared spectra of the two samples were identical.

3,3-Dimethoxy-5α-androstan-17β-ol Acetate (7) from 17β-Acetoxy-5α-androstan-3-one.—A solution of 2.0 g. (6.0 mmoles) of 17β-acetoxy-5α-androstan-3-one, m.p. 155–158°, 5 ml. of benzene, 1 ml. of methyl orthoformate, 0.75 ml. of methanol, and 1 drop of 9.8 *N* ethanolic hydrogen chloride was refluxed for 2 hr. The solution was made alkaline with methanolic potassium hydroxide, and ether and water were added. The organic layer was separated, washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and then con-

centrated to dryness. The white crystalline residue was recrystallized from acetone to give 1.77 g. (78%) of the dimethyl ketal **7**, m.p. 141–145°. Its infrared spectrum was identical with that of the sample prepared in a previous experiment and the mixture melting point of the two samples was not depressed.

Attempted Reaction of 2α-Iodo-17β-acetoxyandrost-4-en-3-one (8) with Mercaptoacetamide.—A solution of 3.9 g. (8.6 mmoles) of the iodo ketone **8**, m.p. 124–126°, 1.2 g. (13 mmoles) of mercaptoacetamide, and 2.1 g. of γ-collidine in 80 ml. of acetonitrile was refluxed for 48 hr. under nitrogen. The solvent was removed by warming *in vacuo* and the residue was taken up in methylene dichloride and poured onto a column containing 120 g. of silica gel. Elution with ether afforded material which was recrystallized from acetone–hexane to give 2.25 g. of starting compound (**8**), m.p. 138–140°, apparently a polymorph of the lower melting form. The melting point was 125–128° upon admixture with a sample of the lower melting form, and the infrared spectra of the two samples were identical.

Selective Reduction of Adrenosterone to 17β-Hydroxyandrost-4-ene-3,11-dione (9).[10]—To a solution of 40.6 g. of adrenosterone[10] in 8 l. of absolute ethanol was added a solution of 1.92 g. of sodium borohydride in 30 ml. of water. An additional 10 ml. of water was used to rinse the addition vessel. The solution was stirred at room temperature for 1.5 hr., and then 14.5 ml. of acetic acid was added. The bulk of the ethanol was removed by warming *in vacuo*, the residue was dissolved in 1500 ml. of hot benzene, and filtered through Filtercel. The filtrate was concentrated and the residue was recrystallized from acetone–hexane to give 27.6 g. of the 17β-alcohol (**9**), m.p. 181–183.5°. The mother liquor afforded a second crop (4.6 g.), m.p. 174–178°, which was recrystallized from acetone–hexane to give 3.1 g. of product, m.p. 184–186° (75% total yield).

17β-Acetoxy-5β-androstane-3,11-dione (10a) and 17β-Acetoxy-5α-androstane-3,11-dione (11a).—To a solution of 16.7 g. (55 mmoles) of 17β-hydroxyandrost-4-ene-3,11-dione (**9**) in 300 ml. of 95% ethanol was added 1.0 g. of 10% palladium on carbon and the mixture was shaken at room temperature with hydrogen at 54 p.s.i.g. (3.8 kg./cm.^{2}). Hydrogen uptake ceased after 1 molar equiv. was absorbed (10 min.). The catalyst was removed by filtration through Filtercel, and the filtrate was concentrated by warming *in vacuo*. The residue was taken up in methylene dichloride and the solution was dried over powdered magnesium sulfate, then evaporated to dryness. The residual white crystalline solid was dissolved in 25 ml. of acetic anhydride and 50 ml. of pyridine and the solution was kept overnight at room temperature, then poured into water. The product was extracted with methylene dichloride. The extract was washed with water and saturated salt solution and dried over powdered magnesium sulfate, then concentrated to give a crystalline residue which was chromatographed on 600 g. of silica gel. Elution with 10% methylene dichloride–25% ether–65% pentane afforded crystalline material which was recrystallized from acetone–hexane to give 4.8 g. of the 5α-isomer (**11a**), m.p. 159–161°. Concentration of the mother liquor afforded an additional 1.0 g. of this isomer, m.p. 155–158° (30% total yield). The analytical sample, which was prepared by recrystallization from acetone–hexane, melted at 158–160°, $[\alpha]^{25}D$ +37.9° (1% in acetone).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.9; H, 8.5.

Further elution with the same solvent mixture afforded material which was recrystallized from acetone–hexane to give 1.85 g. of the 5β-isomer (**10a**), m.p. 193–200°. A second crop of 2.2 g., m.p. 192–197°, was obtained (21%). The analytical sample, which was prepared by recrystallization from acetone–hexane, melted at 197–199.5°, $[\alpha]^{25}D$ +35.4°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.9; H, 8.7.

17β-Hydroxy-5β-androstane-3,11-dione (10b).[11]—To a solution of 0.22 g. (0.63 mmole) of 17β-acetoxy-5β-androstane-3,11-dione (**10a**) in 10 ml. of methanol was added 0.5 ml. of 30% potassium hydroxide in water, and the resulting solution was refluxed for 2 hr. The base was neutralized by adding 0.25 ml. of acetic acid, and the bulk of the methanol was removed by warming *in vacuo*. Ether was added, and the organic layer was separated and washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and then evaporated to dryness. Recrystallization of the residual solid from ether–hexane afforded 0.12 g. (63%) of **10b**, m.p. 168–169.5°, $[\alpha]^{25}D$ +65.6° (1% in acetone). Herzog,[11] *et al.*, reported m.p. 165–165.5°, $[\alpha]^{25}D$ +65.6° (1% in acetone).

17β-Hydroxy-5α-androstane-3,11-dione (11b).—Hydrolysis of 12.3 g. (35 mmoles) of 17β-acetoxy-5α-androstane-3,11-dione (**11a**) in the manner just described for the 5β-epimer afforded a solid residue which was recrystallized from acetone–hexane to give 8.85 g. of **11b**, m.p. 193–196°. Concentration of the mother liquor afforded an additional 1.25 g. which melted at 192–195° (94%). One recrystallization of the first crop from acetone–hexane afforded a sample which melted at 195.5–198°, $[\alpha]^{25}D$ +71.6° (1% in acetone).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.7; H, 9.5.

2α-Bromo-17β-acetoxy-5α-androstane-3,11-dione (12).—To a stirred solution of 0.56 g. (1.6 mmoles) of 17β-acetoxy-5α-androstane-3,11-dione (**11a**) in 5 ml. of acetic acid containing 1 drop of 30% hydrogen bromide in acetic acid was added dropwise a solution of 0.26 g. (1.6 mmoles) of bromine and 0.12 g. (slightly less than 1 equiv.) of fused sodium acetate in 10 ml. of acetic acid. Then the solution was poured into water and the aqueous mixture was extracted with ether. The layers were separated, and the ether layer was washed with water and saturated salt solution, and dried over anhydrous magnesium sulfate, then concentrated to dryness to give a white crystalline residue. Recrystallization from acetone–hexane afforded 0.45 g. (66%) of **12**, m.p. 172–173.5°. The analytical sample, which was prepared by recrystallization from acetone–hexane, melted at 178–179°, $[\alpha]^{25}D$ +47.3° (1% in acetone).

Anal. Calcd. for $C_{21}H_{29}BrO_4$: C, 59.29; H, 6.87; Br, 18.79. Found: C, 59.3; H, 6.9; Br, 19.2.

17β-Acetoxy-11-oxo-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (13).—A solution of 2.26 g. (5.3 mmoles) of 2α-bromo-17β-acetoxy-5α-androstane-3,11-dione (**12**), 0.72 g. (7.9 mmoles) of mercaptoacetamide, and 1.8 ml. of γ-collidine in 100 ml. of acetonitrile was refluxed under nitrogen for 24 hr. The solution was cooled, and the precipitate which separated was collected and washed with acetonitrile to give 0.82 g. (37%) of **13**, m.p. 328–330° dec. (evac. cap., uncorr.). The analytical sample, which was prepared by recrystallization from acetonitrile, melted at 330–331° dec. (evac. cap., uncorr.), $[\alpha]^{25}D$ +5.3°; λ_{max} 230 mμ (ε 4000) and 298 (2600).

Anal. Calcd. for $C_{23}H_{31}NO_4S$: C, 66.15; H, 7.48; S, 7.68. Found: C, 65.9; H, 7.2; S, 7.9.

17β-Acetoxy-5α-androst-1-ene-3,11-dione (14).—To a solution of 1.00 g. (2.35 mmoles) of 2α-bromo-17β-acetoxy-5α-androstane-3,11-dione (**12**) in 10 ml. of dimethylformamide was added 0.69 g. of lithium carbonate and 0.79 g. of lithium bromide and the mixture heated on a steam bath with stirring for 16 hr. The mixture was cooled and 250 ml. of ether and 50 ml. of 2 *N* hydrochloric acid were added. The layers were separated; the organic layer was washed with saturated sodium bicarbonate solution, water, and saturated salt solution, dried over anhydrous magnesium sulfate, and then evaporated to dryness. The residue was recrystallized from acetone–hexane to give 0.76 g. (94%) of the title compound, m.p. 168–171° (uncorr.). The analytical sample, which was prepared by recrystallization from acetone–hexane, melted at 167–168.5°, $[\alpha]^{25}D$ +72.3° (1% in acetone); λ_{max} 228 mμ (ε 10,800).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.1; H, 8.2.

2α-Carbomethoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15).—A solution of 35.6 g. (0.087 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one (**2a**), 16 g. (0.151 mole) of methyl mercaptoacetate, and 20 ml. of γ-collidine in 1 l. of acetonitrile was refluxed for 24 hr. under nitrogen. The solution was concentrated by warming *in vacuo* and the residue was partitioned between 600 ml. of water and 1100 ml. of a 10:1 ether–methylene dichloride solution. The organic layer was separated and washed with 2 *N* hydrochloric acid, 10% sodium carbonate solution, water, and saturated salt solution, and dried over anhydrous magnesium sulfate. Concentration of the solution to *ca.* 250 ml., cooling, and filtering afforded 16.5 g. of **15**, m.p. 142.5–145°. The mother liquor, on concentration and addition of pentane, gave 6.8 g. of this product, m.p. 136–141°, which was recrystallized from acetone to give an additional 5.45 g. of **15**, m.p. 142.5–144° (58% total yield). The analytical sample, which was prepared by recrystallization from acetone, melted at 143–145.5°, $[\alpha]^{25}D$ +22.2°.

Anal. Calcd. for $C_{24}H_{36}O_5S$: C, 66.02; H, 8.31; S, 7.34. Found: C, 66.0; H, 8.0; S, 7.7.

17β-Acetoxy-5α-androstano[2,3-*e*]-2,3-dihydro-1′,4′-oxathiin-2′-one (16).—A solution of 0.50 g. (1.2 mmoles) of 2α-carbo-

methoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15) in 50 ml. of benzene containing 0.1 g. of *p*-toluenesulfonic acid was refluxed for 24 hr. using a water separator. The solution was diluted with 75 ml. of benzene and washed with water and saturated salt solution, and dried over anhydrous magnesium sulfate. Evaporation to dryness and recrystallization of the residue from acetone afforded 0.25 g. (54%) of **16**, m.p. 205–209°. Two further recrystallizations from acetone gave the analytical sample, m.p. 209–210°, $[\alpha]^{25}D$ +6.0°; λ_{max} 281 mμ (ε 1400).

Anal. Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.92. Found: C, 67.9; H, 8.1; S, 7.9.

2-Carbomethoxymethylmercapto-5α-androst-2-ene-3,17β-diol Diacetate (17).—A solution of 3.0 g. (6.9 mmoles) of 2α-carbomethoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15) in 30 ml. of acetic anhydride and 3 ml. of acetyl chloride was refluxed for 3 hr. and then poured into cold water. The aqueous mixture was extracted with 3 portions of ether and the combined extracts were washed with saturated sodium bicarbonate, water, and saturated salt solution, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The residual oil was crystallized from ether–pentane to give 2.3 g. (77%) of enol acetate **17**, m.p. 111–113°. Two recrystallizations from ether–pentane afforded the analytical sample, m.p. 111.5–113.5°, $[\alpha]^{25}D$ +31.7° (1% in acetone).

Anal. Calcd. for $C_{26}H_{38}O_6S$: C, 65.24; H, 8.00; S, 6.70. Found: C, 65.5; H, 7.9; S, 6.9.

17β-Acetoxy-5α-androstano[3,2-*e*]-1′,4′-thiaz-5′-en-3′-one (3a) from 2α-Carbomethoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15).—Ammonia was bubbled into a solution of 1.20 g. (2.75 mmoles) of keto ester **15** in 125 ml. of acetonitrile for 65 min., and the solution was kept at room temperature overnight. Ammonia was again bubbled through the solution for 3 hr. and the solution left for an additional 24 hr. at room temperature. A small amount of flocculent precipitate was removed by filtration, and the filtrate was concentrated to a small volume, cooled, and the precipitate collected to give 0.10 g. (9%) of thiazenone **3a**, m.p. 327–330° dec. (evac. cap.). One recrystallization from acetonitrile afforded a sample, m.p. 328–332° dec. (evac. cap.), which had an infrared spectrum identical with that of a sample prepared in a previous experiment from bromoketone **2a**, and the mixture melting point of the two samples was not depressed.

When the reaction was carried out by dissolving keto ester **15** in methanol at slightly below reflux temperature and bubbling ammonia into the solution for 10 min., then cooling and collecting the precipitate, a 43% yield of thiazenone **3a** was obtained.

2α-Carbomethoxymethylmercapto-5α-androstan-3β,17β-diol 17-Acetate (19) and 17β-Acetoxy-2β,3α,5α-androstano[2,3-*c*]-1′,4′-oxathian-2′-one (18).—To a solution of 25.2 g. (0.100 mole) of lithium tri-*t*-butoxyaluminohydride in 225 ml. of tetrahydrofuran which was cooled in an ice bath was added dropwise in 55 min. a solution of 25.2 g. (0.058 mole) of 2α-carbomethoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15) in 130 ml. of tetrahydrofuran. The reaction mixture was stirred mechanically during the addition and for 30 min. longer. Then 7.2 ml. of acetic acid was added and the mixture was concentrated to dryness by warming *in vacuo*. The residue was shaken with methylene dichloride and 1 *N* hydrochloric acid, the entire mixture filtered through Filtercel, and the filtrate diluted with water. The layers were separated, the organic layer was washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The white crystalline residue was recrystallized from methylene dichloride–acetone to give 10.5 g. of oxathianone **18**, m.p. 278–280°. One further recrystallization afforded the analytical sample, m.p. 280–281.5°, $[\alpha]^{25}D$ +146.1°.

Anal. Calcd. for $C_{29}H_{38}O_4S$: C, 67.94; H, 8.43; S, 7.89. Found: C, 68.1; H, 8.4; S, 8.1.

Concentration of the mother liquor from the first recrystallization above afforded 11.5 g. of a crude crystalline residue which was chromatographed on 350 g. of silica gel. Elution with 1:1:5 methylene dichloride–ether–pentane afforded, after recrystallization from acetone, an additional 2.45 g. (53% total yield) of **18**, m.p. 277–280°. Elution with 1:6 methylene dichloride–ether afforded *ca.* 4 g. of crystalline product which was recrystallized from methanol to give 2.75 g. of hydroxy ester **19**, m.p. 114–117°. Concentration and cooling of the mother liquor afforded an additional 0.7 g. of **19**, m.p. 117–119° (14% total yield). Three recrystallizations of the first crop from methanol gave the analytical sample, m.p. 116–118°, $[\alpha]^{25}D$ −21.6°.

Anal. Calcd. for $C_{24}H_{38}O_5S$: C, 65.72; H, 8.73; S, 7.31. Found: C, 66.0; H, 8.6; S, 7.4.

Cyclization of 2α-Carbomethoxymethylmercapto-5α-androstane-3β,17β-diol 17-Acetate (19) to 17β-Acetoxy-2β,3α,5α-androstano[2,3-*c*]-1′,4′-oxathian-2′-one (18).—A solution of 0.38 g. (0.87 mmole) of hydroxy ester **19** in 50 ml. of benzene was refluxed with 0.1 g. of *p*-toluenesulfonic acid monohydrate for 24 hr. using a water separator. The solution was diluted with 75 ml. of benzene, washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The residue was recrystallized from acetone to give 0.27 g. (77%) of oxathianone **18**, m.p. 278–280°. A mixture melting point with a sample prepared directly from **15** in a previous experiment was not depressed.

Hydrolysis of 17β-Acetoxy-5α-androstano[2,3-*c*]-2,3-dihydro-1′,4′-oxathiin-2′-one (15) to 2α-Carboxymethylmercapto-17β-hydroxy-5α-androstan-3-one (20).—A solution of 0.45 g. (1.1 mmoles) of enol lactone **16** in 45 ml. of methanol was treated with 0.45 g. of potassium bicarbonate in 2.25 ml. of water and the resulting solution refluxed for 20 hr. The methanol was removed by warming *in vacuo* and the residue partitioned between ether and water. The aqueous layer was separated and acidified with dilute hydrochloric acid. The solid which separated was collected and dried to give 0.35 g. (83%) of keto acid **20**, m.p. 209–210°. The infrared spectrum was identical with that of a sample prepared by hydrolysis of **18** (see below) and the mixture melting point of the two was not depressed.

Hydrolysis of 2α-Carbomethoxymethylmercapto-17β-acetoxy-5α-androstan-3-one (15) to 2α-Carboxymethylmercapto-17β-hydroxy-5α-androstan-3-one (20).—A solution of 17.7 g. (40 mmoles) of keto ester **15** in 500 ml. of methanol was treated with a solution of 7.5 g. of potassium hydroxide in 20 ml. of methanol and refluxed for 2.5 hr. The bulk of the methanol was removed by warming *in vacuo*, and ether and water were added to the residue. The aqueous layer was separated, acidified with 2 *N* hydrochloric acid, cooled, and the precipitate collected and dried to give 13.5 g. of product, m.p. 184–186°. Recrystallization from aqueous methanol afforded 12.4 g. (81%) of keto acid **20**, m.p. 211–213°. Occasionally, recrystallized material partly melted and resolidified at *ca.* 185°. The analytical sample, which was prepared by recrystallization from aqueous methanol, melted at 213–215°, $[\alpha]^{25}D$ −2.4° (1% in acetone).

Anal. Calcd. for $C_{23}H_{32}O_4S$: C, 66.28; H, 8.48; S, 8.46. Found: C, 66.5; H, 8.6; S, 8.3.

Reduction of 2α-Carboxymethylmercapto-17β-hydroxy-5α-androstan-3-one (20) to 2α-Carboxymethylmercapto-5α-androstane-3β,17β-diol (21).—A solution of 0.25 g. (0.66 mmole) of keto acid **20** in 2.5 ml. of tetrahydrofuran was cooled in an ice bath and stirred as a solution of 1.0 g. (3.9 mmoles) of lithium tri-*t*-butoxyaluminohydride in 8 ml. of tetrahydrofuran was added in one portion. The ice-cooled solution was stirred for 2 hr. longer and then poured into 80 ml. of 5% acetic acid in water. The mixture was extracted twice with 2:1 methylene dichloride–ether and once with methylene dichloride and the combined organic extracts were washed with water and saturated salt solution and dried over anhydrous magnesium sulfate. Concentration to dryness and recrystallization of the white crystalline residue from aqueous methanol afforded 0.12 g. (48%) of hydroxy acid **21**, m.p. 166–169°. The analytical sample, which was prepared by recrystallization from acetone, melted at 168.5–169°, $[\alpha]^{25}D$ −39.3° (0.5% in acetone).

Anal. Calcd. for $C_{23}H_{34}O_4S$: C, 65.93; H, 8.96; S, 8.38. Found: C, 65.9; H, 8.9; S, 8.4.

Hydrolysis of 2α-Carbomethoxymethylmercapto-5α-androstane-3β,17β-diol 17-Acetate (19) to 2α-Carboxymethylmercapto-5α-androstane-3β,17β-diol (21).—To 0.17 g. (0.39 mmole) of hydroxy ester **19** in 7.5 ml. of methanol was added 0.1 g. of potassium hydroxide in 0.25 ml. of water and the resulting solution was refluxed for 1 hr. The methanol was removed by warming *in vacuo*, and the residue was partitioned between ether and water. The aqueous layer was separated and acidified with 2 *N* hydrochloric acid and then extracted with 2:1 methylene dichloride–ether. The extract was washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The white crystalline residue was recrystallized from aqueous methanol to give 0.07 g. (47%) of hydroxy acid **21**, m.p. 165–168°. The infrared spectrum was identical with that of a sample prepared in the previous experiment by reduction of **20**, and the mixture melting point of the two samples was not depressed.