crystallized from ethyl acetate and from methanol to give 69 mg. of VIII, m.p. 180–185°. This material contained 0.25 atom of deuterium per molecule.

1α,11α-Epoxypregnenolone Acetate. From 11α-Hydroxypregnenolone 3-Acetate.—To a hot solution of 0.75 g. of 11α-hydroxypregnenolone 3-acetate in 300 ml. of cyclohexane was added 4.0 g. of lead tetraacetate. The mixture was allowed to stir and reflux for 4 hr. and was then cooled and filtered. The filtrate was washed with 5% potassium iodide solution, 5% sodium thiosulfate solution, and water, and was dried over anhydrous sodium sulfate. Chromatography of the solution over Florisil resulted in the product fraction being eluted with 7.5% acetone in petroleum ether (b.p. 60–70°). Crystallization of this material from acetone gave 240 mg. product, m.p. 150–157°. The analytical sample had m.p. 152–157°, $[\alpha]_D$ −20° (chloroform).

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 74.16; H, 8.66. Found: C, 73.55; H, 8.62.

From 11β-Hydroxypregnenolone 3-Acetate.—Reaction of 0.96 g. of 11β-hydroxypregnenolone 3-acetate with 7.0 g. of lead tetraacetate for 15 hr. as described previously for the 11α-hydroxy epimer, resulted in 113 mg., m.p. 142–155°, of epoxide being obtained. The analytical sample had m.p. 149–155°, $[\alpha]_D$ −17° (chloroform).

Anal. Found: C, 74.36; H, 9.06.

There was no depression in melting point when the two epoxide samples were mixed and the infrared curves of the two were identical.

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Steroids with Functional Sulfur Groups. III.[1] The Reaction of Some Thiocyano Steroids

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The reaction of 9α-thiocyano-Δ⁴-androstene-3,11,17-trione with aqueous methanolic potassium carbonate gave 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androsten-11β-ol-3,17-dione (VIa). The latter was isomerized to 2′-methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,9α]androstane-3,11,17-trione (Xa) and could be transformed to 9α-methylthio-Δ⁴-androstene-3,11,17-trione (VIIa). Similar reactions were carried out on cortisone and testosterone derivatives.

In a previous paper[1a] we reported that treatment of 9α-thiocyanocortisone acetate (Ia) with aqueous methanolic potassium carbonate at room temperature gave a crystalline compound which was thought to be 9α-thiocarboxamidocortisone (Ib). The absence of an 11-carbonyl band in the infrared spectrum of this compound, however, made such a formulation (Ib) improbable, but unfortunately all attempts at structural elucidation by further chemical transformations failed.

It could be expected that analogous reactions with appropriate compounds lacking the sensitive ketol side chain would give more favorable results. A suitable starting material appeared to be 9α-thiocyano-Δ⁴-androstene-3,11,17-trione (Va), obtained by treatment of the known[4] 9β,11β-epoxy-Δ⁴-androstene-3,17-dione (III) with thiocyanic acid and subsequent oxidation of the resulting 9α-thiocyano-Δ⁴-androsten-11β-ol-3,17-dione (IV) with chromic acid. Treatment of Va with aqueous methanolic potassium carbonate at room temperature gave in a good yield, a product exhibiting absorption maxima at 3.01 μ (hydroxyl), 5.73 μ (C-17 carbonyl), 5.99 μ (Δ⁴-C-3 carbonyl), 6.07 μ (C=N),[5] 6.11 (Δ⁴ C=C), but lacking the absorption bands ascribed to the C-11 carbonyl (5.86 μ) and the thiocyano groups (4.64 μ). The hydroxyl moiety of this compound could not be acetylated with pyridine–acetic anhydride. Furthermore, analytical data agreed with the empirical formula $C_{21}H_{27}O_4NS$ (Va + CH_3OH) rather than $C_{20}H_{25}O_4NS$ (Va + H_2O) and indicated the presence of a methoxyl group. The appearance of a singlet peak at τ 6.15[6] in the n.m.r. spectrum also supported the above observation. In view of this evidence, we are assigning to this product the provisional structure 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androsten-11β-ol-3,17-dione (VIa), and by analogy ascribing the formulation 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (IIa) to the reaction product of Ia. If aqueous ethanolic potassium carbonate is used in place of methanolic potassium carbonate, the corresponding 2′-ethoxythiazolino derivative, VIc,[7] is formed. The presence of the ethoxyl function was shown by elementary analysis as well as n.m.r. data [τ 5.78 (quartet) and τ 8.70 (triplet)].[6]

Treatment of VIa in aqueous ethanolic potassium carbonate at reflux afforded, instead of the expected 9α-thiol derivative, an easily sublimable product which gave a negative sodium nitroprusside test. The infrared spectrum of this compound exhibited bands at 5.73, 5.91, and 6.03 μ, attributable to C-17, C-11, and Δ⁴-C-3-carbonyls, respectively, and lacked the SH absorption,[8] as would be expected of 9α-methylthio-Δ⁴-

(1) (a) Part I, T. Kawasaki and E. Mosettig, *J. Org. Chem.*, **27**, 1374 (1962); (b) Part II, Y. Ueda and E. Mosettig, to be published.

(2) Visiting Scientists, National Institutes of Health, under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute.

(3) Deceased on May 31, 1962.

(4) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(5) L. C. King, L. A. Subluskey, and E. W. Stern, *J. Org. Chem.*, **21**, 1232 (1956); A. I. Meyers, *ibid.*, **24**, 1233 (1959); **26**, 218 (1961).

(6) A singlet peak at τ 6.17–6.20 is observed for the CH_3O function in a similar environment, *i.e.* —C≡C—OCH_3. Two peaks at 8.70 (triplet) and 5.73 (quartet) are observed with C_2H_5O function in CH_3CH_2O—C(=O)—. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 105, 291, 107, 181, etc.

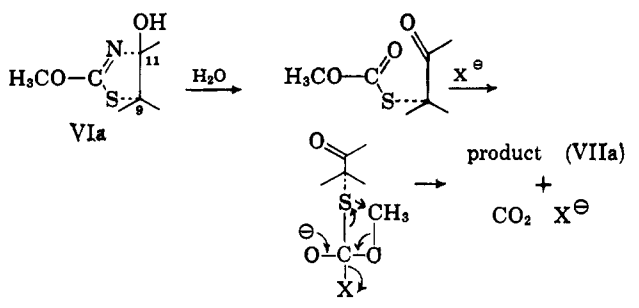
(7) Further transformation of the ethoxythiazolino compound is now under study.

(8) At 2000–2550 cm.⁻¹: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 350.

androstene-3,11,17-trione (VIIa).[9] The n.m.r. data corroborated this structural assignment. In addition to the methyl groups at C-18 (τ 9.06) and C-19 (τ 8.51), there appeared a singlet at τ 7.99 attributable to the S-methyl[10,11] at C-9. Enol acetylation of the product gave 9α-methylthio-$\Delta^{3,5}$-androstadien-3-ol-11,17-dione acetate (VIII), easily hydrolyzable to the original compound (VIIa) by aqueous methanolic potassium carbonate at room temperature. Similarly the treatment of compound IIa with aqueous ethanolic potassium carbonate at reflux afforded 9α-methylthiocortisone (VIIc). The n.m.r. spectrum of its 21-acetate, VIId, showed the presence of an S-methyl function at τ 7.93 (singlet)[10,11] as in VIIa.

Upon refluxing a methanolic solution of VIa, a compound which exhibited absorption maxima at 5.73 μ

(9) This transformation may proceed as shown; however, further study is obviously required for clarification.



(10) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 46, 144; A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, Jr., *J. Am. Chem. Soc.*, **84**, 3897 (1962).

(11) 7α-Methylthiotestosterone acetate exhibits a band at τ 7.94 (singlet). We are greatly indebted to Drs. M. J. Weiss, H. Kissman, and R. E. Schaub (Lederle Laboratories, American Cyanamide Co., Pearl River, N. Y.) for providing us with a sample of the compound.

(C-17 carbonyl), 5.84 μ (C-3 and C-11 carbonyls), 6.10 μ (C=N)[5] was obtained in a good yield. It possessed no absorption maximum in the ultraviolet spectrum and both analytical and n.m.r. data (τ 6.29[6]) indicated the presence of a methoxy function. The appearance of two six-membered ring ketone absorption bands and the absence of both the hydroxyl at C-11 and the α,β-unsaturated carbonyl absorption bands at C-3 in the infrared spectrum of the newly formed compound have led us to propose tentatively the formulation 2′-methoxy-5′,6′-dihydro-4′H-thiazino-[4′,5′,6′:5α,10,9α]androstane-3,11,17-trione (Xa) as the structure for this product. This rearrangement involving the rupture of a C_{11}–N bond of the thiazoline ring and reattachment at C-5 with formulation of a dihydrothiazine ring is a novel one hitherto unobserved in the steroid field.[12] Further studies of these compounds are being pursued. Treatment of Xa with sodium borohydride in pyridine at room temperature yielded predominantly a reduction product of the 17-keto function, 2′-methoxy-5′,6′-dihydro-4′H-thiazino[4′,5′,6′:5α,10,9α]androstan-17β-ol-3,11-dione (Xb). The bulky α-oriented thiazine ring in Xa is probably responsible for the selective reduction of the carbonyl at C-17 in preference to the one at C-3.[13] The C-3 ketone was proved intact by further conversion to the 2,4-dinitrophenylhydrazone derivative, Xd. A similar isomerization of 2′-methoxythiazolino[4′,5′:11α,9α]hydrocortisone (IIa,b) occurred by refluxing in methanol, yielding the 2′-methoxy-5′,6′-dihydro-4′H-thiazino compounds, IXa,b. The isomerization of IIa to IXa was also accomplished by allowing an ethanolic solution of IIa to stand for a long time at room temperature, or by fusing IIa at 178–182° for five minutes. Either thiazino compound (IXa and Xa) can be separated from its isomeric precursor, the thiazolino compound, by thin-layer chromatography. Sodium bismuthate oxidation of IXa to Xa correlated the thiazino compounds of the cortisone series to the ones from the androstane series.

For the purpose of biological studies, we have prepared some 17-hydroxy analogs of the previous derivatives. Reduction of Va with sodium borohydride (sixfold excess) gave a 1:2 mixture of 9α-thiocyano-Δ^4-androsten-17β-ol-3,17-dione (Vb) and 9α-thiocyano-Δ^4-androstene-3ξ,17β-diol-11-one (XI); the latter was converted into the former by manganese dioxide oxidation. When the reduction of Va was carried out using a fourfold excess of the hydride, Vb was formed predominantly. The reaction of Vb with aqueous methanolic potassium carbonate at room temperature gave 2′-methoxythiazolino[4′,5′:11α,9α]-Δ^4-androstene-11β,-17β-diol-3-one (VIb), which could be converted into 9α-methylthio-Δ^4-androsten-17β-acetoxy-3,11-dione (VIIb) and Xb by the method described previously. The thiazino compound, Xb, prepared through VIb was shown to be identical with the one obtained by sodium borohydride reduction of Xa.

(12) (a) According to Dreiding stereomodel studies, the possible positions of forming new C–N bonds are C-1, C-5, C-7, C-12, and C-14. Among these C-5 appears to be the most favorable. (b) Further treatment of Xa with aqueous ethanolic potassium carbonate at reflux yielded only the starting compound, thus proving that Xa is not involved as an intermediate in the formation of VIIa from VIa.

(13) The reduction of the C-3 carbonyl function occurs in preference to the one at C-17 in 5α-androstane-3,17-dione; E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2814 (1952).

Biological studies of these analogs are now under way.

Experimental[14]

9α-Thiocyano-Δ^4-androsten-11β-ol-3,17-dione (IV).—To a solution of 9β,11β-epoxy-Δ^4-androstene-3,17-dione (III)[4] (4.21 g.) in glacial acetic acid (70 ml.) was added the thiocyanic acid solution[1a] (70 ml.). The resulting solution was allowed to stand at room temperature for 26 hr., poured into water (500 ml.), and extracted with chloroform. The extracts were washed with water, dried, and evaporated under reduced pressure to an oily residue, which was crystallized from acetone–hexane giving 2.20 g. (44%) of a product melting at 158.5–160° dec. Recrystallization from the same solvent mixture yielded colorless prisms with m.p. 159–162° dec.; $[\alpha]_D$ +248° (*c* 0.4, dioxane); λ_{max} 242 mμ (ϵ 14,200); 2.92 μ (OH), 4.67 μ (SCN), 5.75, 6.06 μ (CO). In subsequent runs the yield ranged from 25–45%.

Anal. Calcd. for $C_{20}H_{25}O_3NS$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 66.72; H, 7.16; N, 4.03; S, 8.44.

9α-Thiocyano-Δ^4-androstene-3,11,17-trione (Va).—A solution of chromic acid (4.0 g.) in water (75 ml.) was added drop by drop in the course of 20 min. to a stirred solution of IV (2.91 g.) in glacial acetic acid (285 ml.). After addition was completed, stirring was continued for an additional hour and the reaction mixture was poured into water (750 ml.). The washed and dried chloroform extract, after evaporation of the solvent and trituration with acetone, yielded crystalline material (m.p. 206–208° dec.). Additional crystalline material was obtained by adding hexane to the acetone filtrate (m.p. 203–208° dec.). The total yield varied from 74–82%. The analytical sample was obtained by recrystallization with acetone, m.p. 212–215° dec.; $[\alpha]_D$ +453° (*c* 0.37 dioxane); λ_{max} 236 mμ (ϵ 14,270); 4.64 μ (SCN), 5.73, 5.86, 5.99 μ (CO).

Anal. Calcd. for $C_{20}H_{23}O_3NS$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 66.97; H, 6.38; N, 4.28; S, 9.00.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ^4-androsten-11β-ol-3,17-dione (VIa).—To a well stirred suspension of Va (1.01 g.) in methanol (25 ml.) was added a 10% aqueous potassium carbonate solution (2.3 ml.) in an atmosphere of nitrogen. Within 1.5 hr. the original precipitate went into solution and a different crystalline material precipitated from the orange-colored reaction mixture. After addition of glacial acetic acid (0.35 ml.) and water (250 ml.), the reaction mixture was extracted with chloroform. The oily residue, obtained by evaporation of the solvent, was triturated with acetone. The first crop of crystals (0.535 g.) and the second one from the mother liquor (0.153 g.) consisted of nearly pure material; total yield, 63% (in a second experiment 73%). The analytical sample was obtained by recrystallization with acetone; colorless prisms, m.p. 234–235.5°; $[\alpha]_D$ +400° (*c* 0.46); $\lambda_{max}^{dioxane}$ 238 mμ (ϵ 16,930); 3.01 μ (OH), 5.73, 5.99 μ (CO), 6.07 μ (C=N), n.m.r., τ 4.16 (H at C-4), τ 6.15 (CH_3O), τ 8.28 (CH_3 at C-19), τ 8.92 (CH_3 at C-18) were obtained.

Anal. Calcd. for $C_{21}H_{27}O_4NS$: C, 64.76; H, 6.99; N, 3.60; S, 8.22; OCH_3, 7.97. Found: C, 64.95; H, 7.25; N, 3.57; S, 8.21; OCH_3, 7.75.

2′-Ethoxythiazolino[4′,5′:11α,9α]-Δ^4-androsten-11β-ol-3,17-dione (VIc).—Treatment of Va (0.2 g.) with ethanol (40 ml.) and 10% aqueous potassium carbonate solution (4.0 ml.), followed by glacial acetic acid (0.7 ml.), water (400 ml.) as in VIa resulted in the formation of VIc, yield 0.1 g. (45%). The analytical sample was obtained by recrystallization from acetone–hexane, m.p. 209–210°; $[\alpha]_D$ +392° (*c* 0.19); $\lambda_{max}^{dioxane}$ 237.5 mμ (ϵ 15,190); λ_{max}^{KBr} 2.92 μ (OH); 5.74, 6.03 μ (CO), 6.13 μ (C=N); n.m.r., τ 4.15 (H at C-4), τ 5.78 (quartet, CH_2 on EtO), τ 8.73 (triplet, CH_3 on EtO), τ 8.28 (CH_3 at C-19), τ 8.91 (CH_3 at C-18).

Anal. Calcd. for $C_{22}H_{31}O_4NS$: C, 65.15; H, 7.71; N, 3.45; S, 7.91; C_2H_5O, 11.11. Found: C, 65.55; H, 7.29; N, 3.14; S, 7.57; C_2H_5O, 11.13.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ^4-pregnene-11β,17α,21-triol-3,20-dione (IIa).—9α-Thiocyano-Δ^4-pregnene-17α,21-diol-3,-11,20-trione acetate[1] (1.0 g.) was treated with methanol (21 ml.)

(14) All melting points were determined on a Kofler block and recorded as read. Optical rotations were measured in chloroform at 20° unless mentioned otherwise. The ultraviolet absorption spectra were measured in ethanol solution with a Cary self-recording spectrophotometer Model 11, infrared spectra in Nujol with a Perkin-Elmer double beam spectrophotometer Model 21 unless specified otherwise. Nuclear magnetic resonance spectra in deuteriochloroform with a Varian A-60.

and 10% aqueous potassium carbonate (2.1 ml.) for 1.3 hr. as in VIa, then treated with glacial acetic acid (0.33 ml.) and water (240 ml.), followed by extraction with ethyl acetate. The evaporation of the solvent left a solid residue which was recrystallized from acetone; yield, 0.471 g. (48%). The analytical sample melted at 160–163° (with previous softening followed by bubbling) only to solidify and melt again at 230–233°; $[\alpha]_D$ +299° (*c* 0.24); $\lambda_{max}^{dioxane}$ 237 mμ (ε 14,170); 2.92, 3.14 μ (OH), 5.83, 6.03 μ (CO), 6.16 μ (C=N).

Anal. Calcd. for $C_{23}H_{31}O_6NS$: C, 61.45; H, 6.95; N, 3.12; S, 7.12; OCH_3, 6.90. Found: C, 61.00; H, 7.24; N, 3.16; S, 7.08; OCH_3, 6.91.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione Acetate (IIb).—IIa (0.2 g.) was acetylated with pyridine (4 ml.) and acetic anhydride (2 ml.). The analytical sample was obtained by recrystallization from acetone–hexane. The compound melted at 201° (with bubbling), solidified, and melted again at 265–269°; $[\alpha]_D$ +347° (*c* 0.29); $\lambda_{max}^{dioxane}$ 237 mμ (ε 15,190); 3.00 μ (OH), 5.69, 5.77, 6.05 μ (CO), 6.15 μ (C=N).

Anal. Calcd. for $C_{25}H_{33}O_7NS$: C, 61.08; H, 6.75; N, 2.85; S, 6.52; OCH_3, 6.31; CH_3CO, 8.76. Found: C, 61.32; H, 7.08; N, 2.60; S, 6.73; OCH_3, 5.79; CH_3CO, 9.0.

9α-Methylthio-Δ⁴-androstene-3,11,17-trione (VIIa).—To a suspension of VIa (0.6 g.) in ethanol (72 ml.) was added a 10% aqueous potassium carbonate solution (27 ml.) (previously saturated with nitrogen), and the mixture was heated at 85–90° for 20 min. with nitrogen aeration. The cooled reaction mixture was acidified with glacial acetic acid (9 ml.), poured into water (600 ml.), and extracted with chloroform. Evaporation of the extract, followed by trituration of the residue with 10 ml. of methanol, gave VIIa (0.29 g.) melting at 209–211° (acetone–hexane); yield, 53%. (In other runs, yields ranged between 48–60%.) The analytical sample melted at 232–236° (colorless prisms from methanol); $[\alpha]_D$ +493° (*c* 0.46); λ_{max} 239.5 mμ (ε 16,550); λ_{max}^{KCl} 5.73, 5.91, 6.03 μ (CO); n.m.r., τ 4.15 (H at C-4), τ 7.99 (SCH_3 at C-9), τ 8.51 (CH_3 at C-19), τ 9.06 (CH_3 at C-18).

Anal. Calcd. for $C_{20}H_{26}O_3S$[15]: C, 69.33; H, 7.56; S, 9.25. Found: C, 69.30; H, 7.26; S, 9.12.

9α-Methylthio-Δ³,⁵-androstadien-3-ol-11,17-dione Acetate (VIII).—A solution of VIIa (0.458 g.) and *p*-toluenesulfonic acid monohydrate (0.1 g.) in acetic anhydride (12 ml.) was allowed to stand at room temperature overnight and poured into ice–water. The solid precipitate (0.511 g.), after one crystallization from methanol, melted at 164–169°. The analytical sample (colorless, thin plates from methanol) melted at 171–174°; $[\alpha]_D$ +164° (*c* 0.223); λ_{max} 235 mμ (ε 17,950); 5.67 (sh), 5.73, 5.90 μ (CO); n.m.r., τ 4.27 (H at C-4), τ 4.50 (H at C-6), τ 7.85 (acetyl CH_3), τ 8.07 (SCH_3 at C-9), τ 8.71 (CH_3 at C-19), τ 9.07 (CH_3 at C-18).

Anal. Calcd. for $C_{22}H_{28}O_4S$; C, 68.01; H, 7.27; S, 8.25; CH_3CO, 11.08. Found: C, 68.01; H, 7.44; S, 8.59; CH_3CO, 11.27.

9α-Methylthio-Δ⁴-pregnene-17α,21-diol-3,11,20-trione (VIIc).—IIa (0.303 g.) was treated with ethanol (24 ml.) and 10% aqueous potassium carbonate (9 ml.) as in VIIa for 15 min., followed by treatment with glacial acetic acid (3 ml.) and water (200 ml.). The compound (VIIc) was extracted from the reaction mixture with ethyl acetate. The extract was washed, dried, and evaporated to dryness to afford a yellow crystalline residue, which was recrystallized from acetone; yield, 0.094 g. (34.2%). The analytical sample was obtained by recrystallization from methanol and then with acetone, m.p. 257–259°; $[\alpha]_D$ +357° (*c* 0.22, dioxane); λ_{max} 240 mμ (ε 14,920); 2.89, 2.95 μ (OH), 5.84, 5.88, 6.04 μ (CO).

Anal. Calcd. for $C_{22}H_{30}O_5S$; C, 65.00; H, 7.44; S, 7.89. Found: C, 65.08; H, 7.44; S, 8.17.

9α-Methylthio-Δ⁴-pregnene-17α,21-diol-3,11,20-trione Acetate (VIId).—Acetylation of VIIc (0.094 g.) with pyridine (2 ml.) and acetic anhydride (1 ml.) gave a crude acetate (0.072 g.), which was crystallized from acetone–hexane and then from methanol. Colorless needles of m.p. 210–213°; $[\alpha]_D$ +360° (*c* 0.24); λ_{max} 240 mμ (ε 15,110); 2.92 μ (broad, OH), 5.71, 5.78, 5.90, 5.98 μ (CO), were obtained; n.m.r., τ 4.14 (H at C-4), τ 5.07 (quartet, CH_2 at C-21), τ 7.82 (acetyl CH_3), τ 7.93 (SCH_3 at C-9), τ 8.53 (CH_3 at C-19), τ 9.28 (CH_3 at C-18).

Anal. Calcd. for $C_{24}H_{32}O_6S$; C, 64.26; H, 7.19; S, 7.15; CH_3CO, 9.60. Found: C, 64.05; H, 7.49; S; 7.60; CH_3CO, 10.03.

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]androstane-3,11,17-trione (Xa).—A. A suspension of VIa (0.29 g.) in methanol (50 ml.) was refluxed for 27 hr. and the resulting solution was concentrated and allowed to cool. Recrystallization of the crystalline precipitate from methanol gave colorless thin rods of Xa melting at 225–226°; $[\alpha]_D$ +268° (*c* 0.50); in the ultraviolet spectrum end-absorption only, λ_{max} 5.73, 5.84 μ (CO), 6.10 μ (C=N); n.m.r., τ 6.29 (CH_3O), τ 8.38 (CH_3 at C-19), τ 9.14 (CH_3 at C-18).

Anal. Calcd. for $C_{21}H_{27}O_4NS$; C, 64.76; H, 6.99; N, 3.60; S, 8.22; CH_3O, 7.97. Found: C, 64.84; H, 7.27; N, 3.69; S, 8.05; CH_3O, 7.95.

B. A suspension of IXa (0.202 g.) and sodium bismuthate (1.6 g.) in glacial acetic acid (20 ml.) and water (20 ml.) was stirred in the dark at room temperature for 7.5 hr. After filtration, the brown precipitate and the colorless filtrate were extracted with chloroform. Evaporation of the combined extracts gave a crystalline residue, which was recrystallized from methanol to afford colorless needles (0.036 g.), second crop (0.027 g.). Further recrystallization gave Xa, m.p. 223–224°.

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]androstan-17β-ol-3,11-dione (Xb).—A. A solution of Xa (0.302 g.) and sodium borohydride (0.031 g.) in aqueous pyridine (7.5 ml. of pyridine, 3 drops of water) and was stirred at room temperature for 24 hr. The turbid solution was treated with 5 drops of glacial acetic acid and poured into cold water (150 ml.). After standing overnight, the mixture furnished practically pure crystalline Xb (0.191 g.). Recrystallization from acetone–hexane gave the analytical sample, melting at 247–252°; $[\alpha]_D$ +200° (*c* 0.26); λ_{max} 2.96 μ (OH), 5.84 μ (CO), 6.09 μ (C=N). Gas–liquid chromatography and thin-layer chromatography indicated the homogeneity of the compound.

Anal. Calcd. for $C_{21}H_{29}O_4NS$: C, 64.42; H, 7.47; N, 3.58; S, 8.19; CH_3O, 7.93. Found: C, 64.46; H, 7.61; N, 3.67; S, 8.57; CH_3O, 8.20.

Extraction of the filtrate with chloroform followed by chromatography on alumina [Woelm, neutral, grade II; chloroform–benzene (1:2)] gave crude Xb (0.053 g.) and 0.009 g. of a compound which probably is 2′-methoxy-5′,6′-dihydro-4H′-1′,3′-thiazino[4′,5′,6′:5α,10,9α]androstane-3ξ,17β-diol-11-one (m.p. 130–133°); λ_{max},[16] 3.00 μ (OH), 5.85 μ (CO), 6.02 μ (C=N).

B. A solution of VIb (0.027 g.) in methanol (25 ml.) was refluxed for 24 hr. and evaporated to dryness. / Recrystallization of the crystalline residue from acetone–hexane gave Xb (mixture melting point, infrared spectra, $[\alpha]_D$).

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]androstan-17β-ol-3,11-dione Acetate (Xc).—Acetylation of Xb (0.140 g.) in the usual manner gave the monoacetate Xc, melting at 214–215.5°[17] (colorless rods, acetone–hexane); $[\alpha]_D$ +163° (*c* 0.18); λ_{max} 5.74, 5.84 μ (CO), 6.02 μ (C=N).

Anal. Calcd. for $C_{23}H_{31}O_5NS$: C, 63.72; H, 7.21; N, 3.23; S, 7.40; CH_3O, 7.16; CH_3CO, 9.93. Found: C, 63.70; H, 7.49; N, 3.32; S, 8.02; CH_3O, 7.52; CH_3CO, 10.16.

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]androstan-17β-ol-3,11-dione 2,4-dinitrophenylhydrazone (Xd).—To a solution of Xb (0.05 g.) in 95% ethanol (2.2 ml.) was added a solution of 2,4-dinitrophenylhydrazine reagent[18] (1.65 ml.). After standing overnight, the orange solution deposited a precipitate (0.052 g.), which was crystallized from ethyl acetate–ethanol. Orange leaflets which change into thin plates while melting at 243–244° were obtained. This again remelted at 255–257°.

Anal. Calcd. for $C_{27}H_{33}O_7N_5S$: C, 56.73; H, 5.82; N, 12.25. Found: C, 56.56; H, 6.07; N, 12.38.

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]pregnane-17α,21-diol-3,11,20-trione (IXa).—A. A solution of IIa (1.0 g.) in methanol (100 ml.) was refluxed for 24 hr., concentrated to a volume of 10 ml., and cooled. The crystalline precipitate (0.66 g., 66%; m.p. 250–252° dec.) was recrystallized from methanol to yield colorless plates of IXa, m.p. 252–254°

(15) The molecular weight determination by the Rast method revealed the improbability of a disulfide formulation. Found: 332.1. Calcd. for $C_{20}H_{26}O_3S$: 346.5.

(16) Taken by a Perkin-Elmer Infracord spectrophotometer.

(17) In an allotropic form (leaflets), the compound melts at 195–198°. The substance was homogeneous as indicated by gas–liquid chromatography and thin-layer chromatography.

(18) Prepared with 2,4-dinitrophenylhydrazine (0.4 g.), concentrated sulfuric acid (2 ml.), water (3 ml.), and 95% ethanol (10 ml.).

dec.; $[\alpha]_D$ +199° (*c* 0.21); in the ultraviolet spectrum end absorption only, λ_{max} 5.84 μ (sh), 5.87 μ (CO), 6.03 μ (C=N).

Anal. Calcd. for $C_{28}H_{31}O_6NS$: C, 61.45; H, 6.95; N, 3.12; S, 7.12; CH_3O, 6.90. Found: C, 61.63; H, 7.13; N, 3.26; S, 7.21; CH_3O, 7.16.

B. A solution of IIa (0.05 g.) in ethanol was allowed to stand at room temperature for 2 weeks and evaporated to dryness. The residue was recrystallized from acetone, to afford a product identical (melting point, infrared spectra) with that obtained by procedure A preceding.

C. Compound IIa (0.05 g.) was heated in an oil bath (178–182°) for 10 min., and the product was recrystallized from acetone to yield 0.013 g. of IXa.

2′-Methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,-9α]pregnane-17α,21-diol-3,11,20-trione Acetate (IXb).—A. Acetylation of IXa (0.204 g.) with acetic anhydride and pyridine at room temperature afforded a crude acetate (0.213 g.), which upon recrystallization from methanol yielded colorless needles, m.p. 250–252°; $[\alpha]_D$ +224° (*c* 0.40); in the ultraviolet spectrum end absorption only; λ_{max} 2.94 μ (OH), 5.74 (sh), 5.79 (sh), 5.84 μ (CO), 6.03 μ (C=N).

Anal. Calcd. for $C_{25}H_{33}O_7NS$: C, 61.08; H, 6.75; N, 2.85; S, 6.52; CH_3O, 6.31; CH_3CO, 8.76. Found: C,6 0.90; H, 6.81; N, 2.96; S, 6.92; CH_3O, 6.59; CH_3CO, 8.7.

B. A solution of IIb (0.175 g.) in methanol (35 ml.) was refluxed for 24 hr., concentrated, and allowed to cool. Crystals of IXb (0.114 g.) melting at 250–254° were obtained.

9α-Thiocyano-Δ⁴-androsten-17β-ol-3,11-dione (Vb) and 9α-Thiocyano-Δ⁴-androstene-3ξ,17β-diol-11-one (XI).—A. Sodium borohydride (0.307 g. *ca.* 1.5 eq. mole) was added in the course of 7 min. to a stirred, ice-cooled suspension of Va (1.898 g.) in methanol (380 ml.), and the mixture was stirred then for a total period of 1 hr. The resulting solution was treated with glacial acetic acid (1.1 ml.), stirred for 10 min., and poured into 3 l. of water. Following the addition of sodium chloride (500 g.), the mixture was extracted with chloroform and the combined extract was evaporated to dryness. The residue was recrystallized once from chloroform and then from acetone–hexane to give colorless needles of XI melting at 195–198°[19]; yield, 0.91 g. (48%).

Anal. Calcd. for $C_{20}H_{27}O_3NS$: C, 66.45; H, 7.53; N, 3.88; S, 8.87: Found: C, 66.59; H, 7.78; N, 3.75; S, 8.57.

The chloroform mother liquor, after removal of crystalline XI gave a product which was recrystallized from aqueous ethanol and then methanol to afford Vb (0.568 g.) melting at 168–170° dec. (with previous softening around 115°); yield, 30% $[\alpha]_D$ +404° (*c* 0.32); λ_{max} 237 mμ (ϵ 14,280); 3.01 μ (OH), 4.67 μ (SCN), 5.84, 6.02 μ (CO). In a second run the yield was 43% (XI) and 45% (Vb).

Anal. Calcd. for $C_{20}H_{25}O_3NS$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 66.97; H, 7.23; N, 3.90; S, 8.66.

B. When the reaction was carried out with Va (1.899 g.), methanol (380 ml.), and sodium borohydride (0.2 g.) under the same conditions as before, Vb was formed in 91% yield. In subsequent runs the yield ranged from 87–88%.

(19) The compound melted at 125° with bubbling then partly changed to rods which remelted at 195–198°. The homogeneity was checked by thin-layer chromatography.

C. A suspension of XI (0.5 g.) and manganese dioxide[20] (5.0 g.) in chloroform (100 ml.) was shaken at room temperature for 30 min., filtered, and evaporated to dryness. One crystallization from methanol gave colorless long rods (0.148 g.). Repeated recrystallizations from acetone–hexane, aqueous ethanol, and then with methanol successively gave the analytical sample, Vb identical (melting point, mixture melting point, infrared spectra, $[\alpha]_D$) with the product described previously.

9α-Thiocyano-Δ⁴-androsten-17β-acetoxy-3,11-dione (Vc).—Acetylation of Vb (0.055 g.) with pyridine (1 ml.) and acetic anhydride (0.5 ml.) yielded a crude product (0.056 g.), which was recrystallized from acetone–hexane to afford colorless needles, m.p. 198–200°; $[\alpha]_D$ +326° (*c* 0.35); λ_{max} 237 mμ (ϵ 14,340); 4.65 μ (SCN), 5.77 μ (Ac), 5.84, 5.95 μ (CO).

Anal. Calcd. for $C_{22}H_{27}O_4NS$: C, 65.81; H, 6.78; N, 3.49; S, 7.98; CH_3CO, 10.72. Found: C, 65.59; H, 6.90; N, 3.48; S, 7.84; CH_3CO, 10.97.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androstene-11β,17β-diol-3-one (VIb).—Treatment of Va (3.292 g.) with methanol (90 ml.) and 10% aqueous potassium carbonate (3.46 ml.) for 30 min. as in VIa, followed by glacial acetic acid (1.2 ml.) and water (900 ml.) treatment yielded an amorphous residue after extraction of the reaction mixture with chloroform. Trituration of the residue with benzene gave VIb, which was recrystallized from acetone–hexane to yield minute prisms (2.528 g., 70.4%). The analytical sample melted at 196–197.5° (same solvent mixture); $[\alpha]_D$ +345° (*c* 0.24); $\lambda_{max}^{dioxane}$ 238 mμ (ϵ 15,350); 2.89, 3.00 μ (OH), 6.06 μ (sh) (CO), 6.10 μ (C=N).

Anal. Calcd. for $C_{21}H_{29}O_4NS$: C, 64.42; H, 7.47; N, 3.58; S, 8.19; CH_3O, 7.93. Found: C, 64.64; H, 7.65; N, 3.67; S, 8.24; CH_3O, 7.84.

9α-Methylthio-Δ⁴-androsten-17β-acetoxy-3,11-dione (VIIb).—VIb (0.18 g.) was treated with ethanol (18 ml.) and 10% aqueous potassium carbonate solution (7.0 ml.) for 30 min. as in VIIa, then with glacial acetic acid (2.82 ml.), water (180 ml.), and extracted with chloroform, The amorphous residue, obtained by evaporation of the solvent, was acetylated with pyridine (2 ml.) and acetic anhydride (1 ml.) to give a crude acetate (0.126 g.) which was recrystallized from acetone–hexane. Prisms of m.p. 200–203°; $[\alpha]_D$ +344° (*c* 0.26); λ_{max} 241 mμ (ϵ 13,800); 5.77, 5.88, 5.99 μ (CO) were obtained; n.m.r., τ 4.15 (H at C-4), τ 5.09 (triplet H at C-17), τ 7.93 (acetyl CH_3), τ 7.99 (SCH_3 at C-9), τ 8.52 (CH_3 at C-19), τ 9.17 (CH_3 at C-18).

Anal. Calcd. for $C_{22}H_{30}O_4S$: C, 67.66; H, 7.74; S, 8.21; CH_3CO, 11.02. Found: C, 67.52; H, 7.82; S, 7.83; CH_3CO, 11.32.

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