Alkaline Hydrolysis of IV.—A solution of 50 mg. of IV in 6 ml. of ethanol (containing some undissolved solid) was treated with 0.5 ml. of 5% aqueous sodium hydroxide solution. After stirring for 30 min., a heavy yellow precipitate began to separate. The mixture was stirred for an additional 18 hr. and then was diluted with water and filtered. The bright yellow powder, 43 mg., m.p. 250–252°, was recrystallized from acetone–hexane to give tiny golden flakes of the 3-hydroxydiazepine, m.p. 252–254°.

Anal. Calcd. for $C_{22}H_{30}N_2O_2$ (354.5): C, 74.54; H, 8.53. Found: C, 74.13; H, 8.68.

Methylation of IV.—To a solution of 100 mg. of IV in 15 ml. of ethanol at 0° was added 0.6 ml. of 10% potassium hydroxide solution and 0.07 ml. of methyl sulfate. Solid began to separate after 10 min., and the mixture then was kept at room temperature for 2 hr., diluted with water, acidified, and extracted with chloroform. The yellow solid obtained from the chloroform solution was reacetylated with acetic anhydride and the crude acetate was chromatographed on alumina. Crystallization of the first three fractions (79 mg.) from ether–hexane gave 55 mg. of glistening yellow flakes of IVb, m.p. 219°.

Anal. Calcd. for $C_{25}H_{34}N_2O_3$ (410.5): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.16; H, 8.07; N, 6.55.

Steroids with Functional Sulfur Groups. IV.[1] The Isomerization of Some 2′-Methoxythiazolino[4′,5′:11α,9α]-11β-hydroxy Steroids

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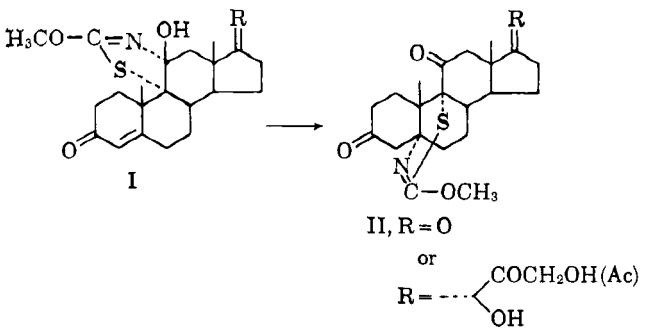
The effect of some modifications in ring A on the course of the rearrangement of 2′-methoxythiazolino[4′,5′:-11α,9α]-11β-hydroxy steroids to 2′-methoxydihydrothiazino steroids was studied. It was found that the α,β-unsaturated oxo system is the minimum requirement for such an isomerization. The Δ[1,4]-dien-3-one system led to the formation of a 2′-methoxydihydrothiazino[4′,5′,6′:1α,10,9α] steroid (X) and a 2′-methoxydihydrothiazino[4′,5′,6′:5α,10,9α] steroid (IX) in the ratio of 7:1.

In a preceding paper,[1c] we reported a novel isomerization reaction involving the rupture of the C–N bond at C-11 of the thiazoline ring and reattachment of the nitrogen bearing function to C-5 with the resultant formation of a dihydrothiazine ring as shown (I → II).



It had appeared to us that this isomerization required the presence of an α,β-unsaturated oxo system in certain proximity to the thiazolino moiety. This study is a partial attempt to define more precisely the scope and limitations of this rearrangement, particularly with respect to ring A of the steroid molecule.

As expected, attempts to rearrange the 3-oxo saturated derivative, 2′-methoxythiazolino[4′,5′:11α,9α]-5α-androstan-11β-ol-3,17-dione (VIIa), to the dihydrothiazino compound did not materialize, thus attesting to the necessity for the presence of unsaturation. The starting material VIIa was prepared from 9β,11β-epoxy-5α-androstane-3,17-dione (IVa) by a similar reaction sequence described previously[1c] for the preparation of I (R = O). Compound IVa was obtained by catalytic hydrogenation of 9β,11β-epoxy-Δ⁴-androstene-3,17-dione (III) over palladium–charcoal in ethyl acetate. The hydrogenation furnished a mixture of isomers whose separation was achieved by chromatography on alumina. As expected from the presence of an 11β-substituent,[3] the 5α isomer was shown to be the predominant product. VIIa, thus prepared, when refluxed in methanol for a period of 24 hr., remained unchanged; however, prolonged refluxing (6 days) yielded a negligible amount of unidentified substance as revealed by thin layer chromatography. When compound VIIa was refluxed in aqueous ethanolic potassium carbonate, 9α-methylthio-5α-androstane-3,11,17-trione (VIII) was formed in accordance with our earlier observation.[1c] A singlet peak at τ 8.05 in the n.m.r. spectrum corroborated[1c] this structural assignment. Further elaboration of the methylthio function to obtain the sulfoxide or sulfone derivative by oxidation with monoperphthalic acid[4] or with the pyridine chromic acid complex[5] failed. An attempt to obtain the 9α-thiocyano compound (VIa) with cyanogen bromide[6] was also unsuccessful.

That the double bond alone is also insufficient for isomerization was shown by the refractoriness of 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androstene-3ξ,11β,17β-triol (VIIc) toward prolonged refluxing (6 days) with methanol. VIIc was prepared by the methanolysis of VIc.[1c] The requirement of an α,β-unsaturated oxo system for isomerization to the dihydrothiazine derivative thus becomes apparent.

It became of some interest to study the effect of a 1,4-dienone system upon the isomerization of the thiazoline moiety. Accordingly, 9β,11β-epoxy-Δ[1,4]-andro-

(1) (a) In remembrance of the late Dr. Erich Mosettig of this Institute; (b) part II, Y. Ueda and E. Mosettig, *Steroids*, **1**, 361 (1963); (c) part III, I. Kitagawa, Y. Ueda, T. Kawasaki, and E. Mosettig, *J. Org. Chem.*, **28**, 2228 (1963).

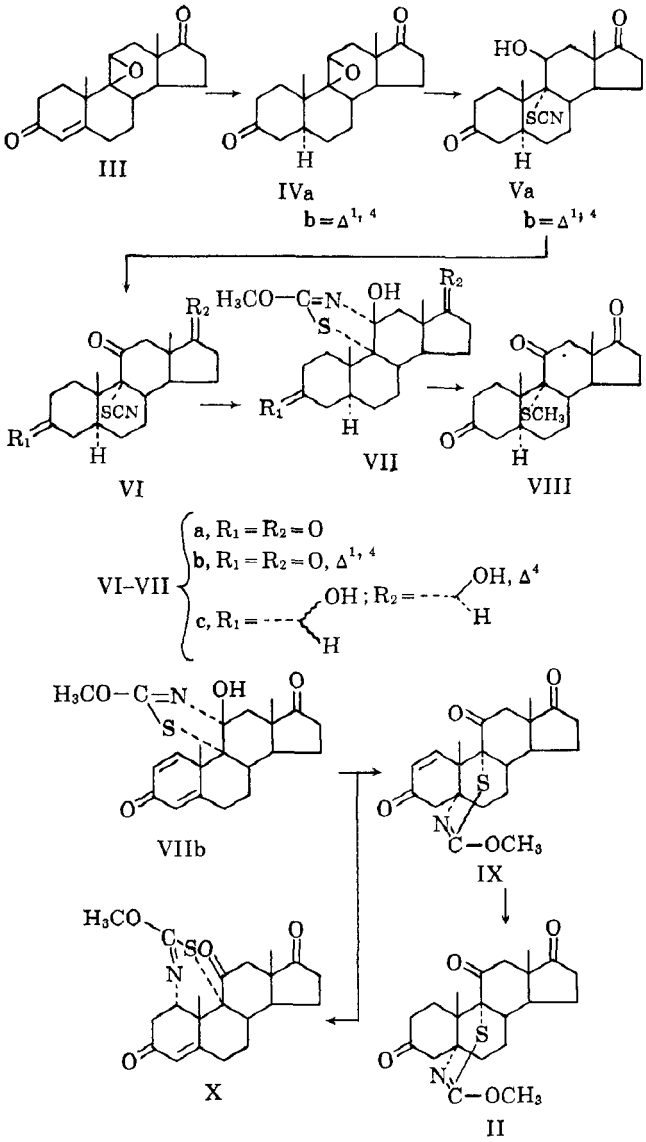
(2) Visiting Scientist (1961–1963), National Institutes of Health, under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute; Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.

(3) J. Pataki, G. Rosenkranz and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(4) R. E. Shaub and M. J. Weiss, *J. Org. Chem.*, **27**, 2221 (1962).

(5) D. Edwards and J. B. Stenlake, *J. Chem. Soc.*, 3272 (1954).

(6) J. von Braun and R. Murjahn, *Ber.*, **59**, 1202 (1926); J. von Braun and P. Engelbertz, *ibid.*, **56**, 1573 (1923).



stadiene-3,17-dione (IVb)[7] was treated with thiocyanic acid[1,8] to afford 9α-thiocyano-$\Delta^{1,4}$-androstadien-11β-ol-3,17-dione (Vb) in a 68% yield. The reaction proceeded rather slowly[9] as compared with the formation of Va or 9α-thiocyano-Δ^4-androsten-11β-ol-3,17-dione.[1c] Chromic acid oxidation of Vb, followed by methanolysis of VIb in base, yielded 2′-methoxythiazolino[4′,5′:11α,9α]-$\Delta^{1,4}$-androstadien-11β-ol-3,17-dione (VIIb).[10] The expected isomerization of VIIb in methanol required a longer period of refluxing than that for the conversion of I to II. Even after refluxing for 7 days, 10% of the starting compound was recovered. The mixture from the isomerization was separated by chromatography on alumina into three components, a major (seven parts) and a minor (one part) product and the starting material (one part). The minor product, exhibiting an ultraviolet absorption maximum at 222.5 mμ[11] (ε 10,700) and infrared bands at 5.72 (C-17 carbonyl), 5.83 (C-11 carbonyl), 6.0 μ (broad,[12] Δ^1-C-3 carbonyl and C=N), is shown to be 2′-methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,9α]-Δ^1-androstene-3,11,17-trione (IX) by its conversion into the known thiazino compound II (R = O)[1c] by catalytic hydrogenation over palladium–charcoal in ethyl acetate. The major product possessed an ultraviolet absorption maximum at 237.5 mμ[13] (ε 12,890) and infrared absorption bands at 5.73 (C-17 carbonyl), 5.86 (C-11 carbonyl), 5.97 μ (broad,[12] Δ^4-C-3 carbonyl, and C=N). To it is ascribed the alternate structure X. N.m.r. data of the two isomers also support these structural assignments. Compound IX exhibited a singlet at τ 6.33 (CH_3O),[1c] a pair of doublets at 4.20 (proton at C-2) and 2.50 (proton at C-1) with J = 10 c.p.s.,[14] in addition to two peaks at 9.12 and 8.30, corresponding to the C-18, C-19 methyls, respectively. On the other hand, isomer X possessed a singlet at τ 4.19 (proton at C-4)[15] in addition to a singlet at 6.34 (CH_3O).[1c]

This apparent difference in the reactivity[16] of positions 1 and 5 in the isomerization of the dienone VIIb was also noted by Dodson and Tweit[17] in their study on the addition of alkanethiolic acids to $\Delta^{1,4}$-3-oxo steroids. They found that the Δ^1 bond is selectively attacked by the nucleophilic alkanethiolic acid ion.

Experimental[18]

9β,11β-Epoxy-5α-androstane-3,17-dione (IVa).—A mixture of *9β,11β-epoxy-Δ^4-androstene-3,17-dione*[19] (*III*, 2.1 g.) and 10% palladium–charcoal (1.05 g.) in ethyl acetate (500 ml.) was hydrogenated at room temperature under atmospheric pressure. The product was purified by chromatography on alumina (Woelm, neutral, grade III, 100 g.) using 1:2 benzene–petroleum ether (b.p. 60–71°) mixture and benzene successively as eluents. Crystallization from acetone–hexane of the later fractions gave colorless crystals of IVa (1.58 g., 73.8%), melting at 166–172°. Repeated crystallization from benzene–hexane yielded an analytical sample melting at 175–176°, $[\alpha]_D$ +98.4° (*c* 0.42); λ_{max} 5.75, 5.83 μ (CO).

(7) Prepared from $\Delta^{1,4,9(11)}$-androstratriene-3,17-dione through the 9,11-bromohydrin according to the procedure developed by K. Tsuda, S. Nozoe, and Y. Okada (forthcoming publication). We wish to express our appreciation for a copy of the manuscript before publication. Physical constants of IVb [m.p. 167–169°, $[\alpha]_D$ +83° (*c* 0.68); found: C, 76.23; H, 7.65] agreed with their data [m.p. 164–169°, $[\alpha]_D$ +88° (*c* 0.71)].

(8) A more effective concentration of thiocyanic acid is needed. See the Experimental section.

(9) The epoxy-ring opening of 9β,11β-epoxy-$\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione by hydrogen fluoride proceeds more slowly than the corresponding 9β,11β-epoxy-Δ^4-pregnene derivative [R. F. Hirschmann, R. Miller, J. Wood, R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956)].

(10) Further transformation of VIIb to a 9α-methylthio derivative failed.

(11) *The calculated value for the ultraviolet absorption maximum of* Δ^1-3-keto steroid is 227 mμ [L. Dorfman, *Chem. Rev.*, **53**, 47 (1953)]. 9α-Fluoro-Δ^1-pregnene-11β,17α,21-triol-3,20-dione acetate was shown to have an ultraviolet absorption maximum at 222 mμ (log ε 4.03) [R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett, M. Tishler, *J. Am. Chem. Soc.*, **77**, 3166 (1955)].

(12) Sufficient resolution could not be obtained even with use of a grating infrared spectrophotometer, Perkin-Elmer Model 421.

(13) Both compounds IX and X exhibit a hypsochromic shift of about 4 ~ 6 mμ from their calculated values.

(14) The spin–spin coupling constant for *cis* olefinic protons is shown to vary from 6–14 c.p.s. [L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85].

(15) The chemical shift of a proton at C-4 in testosterone is shown to be at τ 4.18 [J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)].

(16) Dreiding-stereomodel studies indicate an almost equal accessibility of C-1 or C-5 for the attack by a 9α function.

(17) (a) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959); (b) the isothiocyanate ion also adds predominantly at position 1 to produce 1α-isothiocyano-cortisone-21-acetate [K. Takeda, T. Kubota, J. Kawanami, *Chem. Pharm. Bull.* (Tokyo), **8**, 615 (1960)].

(18) 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 15, infrared spectra in Nujol with a Perkin-Elmer double-beam spectrophotometer Model 21 unless specified otherwise. The n.m.r. spectra were taken in deuteriochloroform with a Varian *A-60 spectrometer*. *Silica gel* G was used for thin layer chromatography.

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

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.62; H, 8.86.

9α-Thiocyano-5α-androstan-11β-ol-3,17-dione (Va).—A solution of IVa (1.0 g.) in glacial acetic acid (20 ml.) and thiocyanic acid solution[20] (20 ml.) was allowed to stand at room temperature for 24 hr. The yellow solution was then treated with ice–water and extracted with chloroform. The extracts yielded an amorphous residue, which was crystallized from acetone–hexane to yield needles melting at 147–150° dec., 0.412 g. (35.2%). The analytical sample was obtained by further recrystallization from the same solvent mixture, m.p. 149–150° dec., $[\alpha]_D$ +94.7° (*c* 0.40, dioxane); λ_{max} 2.88 (OH), 4.65 (SCN), 5.73, 5.85 μ (CO).

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, 7.77; N, 3.66; S, 9.2.

9α-Thiocyano-5α-androstane-3,11,17-trione (VIa).—A stirred solution of Va (0.2 g.) in glacial acetic acid (20 ml.) was treated with chromic acid solution (0.28 g. in 5.0 ml. water) and stirred further for 1 hr. at room temperature. The reaction mixture was then poured into ice-cooled water and allowed to stand in a refrigerator for 2 hr. The colorless crystalline mass was recrystallized from methanol to yield 0.093 g. of leaflets melting at 212–214.5°. Extraction of the aqueous filtrate with chloroform afforded a second crop of leaflets (0.027 g.) melting at 210–212°; total yield, 0.12 g. (60%). The analytical sample was recrystallized from methanol, m.p. 214–215°, $[\alpha]_D$ +273.5° (*c* 0.34, dioxane); λ_{max} 4.66 (SCN), 5.72, 5.86 μ (CO).

Anal. Calcd. for $C_{20}H_{25}O_3NS$: C, 66.82; H, 7.01; N, 3.90; S, 8.99. Found: C, 66.52; H, 7.07; N, 4.09; S, 9.05.

2′-Methoxythiazolino[4′,5′:11α,9α]-5α-androstan-11β-ol-3,17-dione (VIIa).—A colorless suspension of VIa (0.336 g.) in methanol (8.5 ml.) with 10% aqueous potassium carbonate solution (1.56 ml., previously saturated with nitrogen) was stirred under nitrogen atmosphere at room temperature for 2 hr. The mixture was then treated with glacial acetic acid (0.26 ml.), poured into water (100 ml.), and the precipitate crystallized from acetone–hexane to yield colorless prisms (0.266 g., 72.0%) melting at 219–228°. Repeated crystallization from the same solvent mixture afforded an analytical sample, m.p. 226–228°, $[\alpha]_D$ +213.9° (*c*, 0.18); λ_{max} 3.12 (OH), 5.76, 5.86 (CO), 6.16 μ (C=N); n.m.r., τ 6.17 (CH_3O), 8.48 (CH_3 at C-19), 8.94 (CH_3 at C-18).

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, 64.56; H, 7.77; N, 3.99; S, 8.09; CH_3O, 7.86.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androstene-3ξ,11β,-17β-triol (VIIc).—A solution of 9α-thiocyano-Δ⁴-androstene-3ξ,17β-diol-11-one[16] (0.55 g.) in methanol (20 ml.) was treated with 10% aqueous potassium carbonate solution (1.5 ml.) for 1.5 hr., as in VIIa. After the addition of glacial acetic acid (0.25 ml.) and water (200 ml.), the reaction mixture was extracted with ethyl acetate. The residue from the extraction which refused to crystallize[21] was repeatedly precipitated from ethyl acetate to free it of adhering impurities and the recovered substance (m.p. 151–156°, 0.03 g.) subjected to refluxing for 6 days in methanol (10 ml.). Even under this treatment a check by thin layer chromatography [ethyl acetate–water (15 ml.:9 drops), R_f 0.21], indicated that the starting material was substantially unchanged. Compound VIIc had λ_{max} 3.06 (OH), 5.74, 5.78 (weak, ester),[21] 6.15 μ (C=N).

9α-Methylthio-5α-androstane-3,11,17-trione (VIII).—To a suspension of VIIa (0.1 g.) in ethanol (12 ml.) was added a 10% aqueous potassium carbonate solution (4.5 ml., previously saturated with nitrogen), and the colorless mixture heated at 93–94° for 20 min. under nitrogen aeration. The cooled reaction mixture was treated with glacial acetic acid (1.0 ml.), poured into water (100 ml.), and extracted with chloroform. The product was crystallized from acetone–hexane to give VIII (yield, 0.071 g., 79.8%), melting at 170–173°. An analytical sample was prepared by repeated crystallization from the same solvent mixture, m.p. 179–182°, $[\alpha]_D$ +312.3° (*c* 0.53, dioxane); λ_{max} 5.76, 5.87 (shoulder), 5.92 μ (CO); n.m.r., τ 8.05 (SCH_3), 8.72, 9.11 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10; S, 9.20. Found: C, 69.01; H, 8.25; S, 9.25.

9α-Thiocyano-Δ¹,⁴-androstadien-11β-ol-3,17-dione (Vb).—A mixture of 9β,11β-epoxy-Δ¹,⁴-androstadiene-3,17-dione[7] (IVb, 2.13 g.), glacial acetic acid (70 ml.), and thiocyanic acid solution[22] (210 ml.) was stirred continuously at room temperature for 6 days. The resulting yellow suspension yielded 1.82 g. (71.2%) of slight yellow prisms (methanol) melting at 191–195° dec. The analytical sample was obtained by repeated crystallization from methanol and from acetone–hexane, m.p. 202–204° dec., $[\alpha]_D$ +314.3° (*c* 0.68, dioxane); λ_{max} 242 mμ (ε 12,760); 3.14 (OH), 4.66 (SCN), 5.74, 6.03 (CO), 6.20, 6.25 μ (C=C).

Anal. Calcd. for $C_{20}H_{23}O_3NS$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 67.32; H, 6.65; N, 3.95; S, 8.90.

9α-Thiocyano-Δ¹,⁴-androstadiene-3,11,17-trione (VIb).—A solution of Vb (0.482 g.) in glacial acetic acid (40 ml.) was treated with aqueous chromic acid solution (0.56 g. in 10 ml. water) as in VIa. It yielded colorless leaflets (0.362 g., 77.7%, from methanol) melting at 204–207° dec. An analytical sample melted at 203–205° dec., $[\alpha]_D$ +533.9° (*c* 0.43); λ_{max} 238 mμ (ε 13,570); 4.67 (SCN), 5.78, 5.83, 5.97 (CO), 6.15, 6.22 μ (C=C).

Anal. Calcd. for $C_{20}H_{21}O_3NS$: C, 67.58; H, 5.96; N, 3.94; S, 9.02. Found: C, 67.87; H, 6.12; N, 3.87; S, 8.80.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ¹,⁴-androstadien-11β-ol-3,17-dione (VIIb).—Treatment of VIb (0.979 g.) in methanol (25 ml.) with 10% aqueous potassium carbonate solution (2.3 ml.) as in VIIa, followed by addition of glacial acetic acid (0.78 ml.), water (500 ml.), and extraction with ethyl acetate, gave a solid residue, which was crystallized from acetone–hexane to yield prisms (0.760 g., 71.2%). An analytical sample melted at 222–223° dec., $[\alpha]_D$ +412.1° (*c* 0.44); λ_{max} 244 mμ (ε 13,600); 3.00 (OH), 5.81, 6.01 (CO), 6.14 (C=N and C=C), 6.22 μ (C=C); n.m.r., τ 2.56 (d),[23] 3.78 (d, J = 10 c.p.s., proton at C-1 and C-2), 3.85 (proton at C-4), 6.23 (CH_3O), 8.26, 8.77 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50; N, 3.62; S, 8.27; CH_3O, 8.01. Found: C, 65.16; H, 6.38; N, 3.78; S, 8.22; CH_3O, 8.24.

The Isomerization of VIIb into IX and X.—A solution of VIIb (0.40 g.) in methanol (100 ml.) was refluxed continuously for 7 days. During this period, the solution was checked by thin layer chromatography (ethyl acetate–cyclohexane–water, 70:30:0.2). Evaporation of the solvent yielded a resinous residue, which was chromatographed on alumina (Woelm, neutral, grade III, 10 g.) and eluted with the following solvent systems: benzene–hexane (4:1), benzene, and benzene–acetone (1:1). The latter fractions of the benzene–hexane eluates along with the succeeding benzene eluates afforded compound X (0.191 g.) of m.p. 228–235° (acetone–hexane). Unchanged starting material (0.043 g.) was obtained from the benzene–acetone eluates. It was unambiguously identified as VIIb by its melting point, infrared spectrum, specific rotation, and chromatographic behavior (t.l.c.). The earlier fractions of the above chromatography together with the mother liquor from the crystallization of X were combined and rechromatographed on alumina (Woelm, neutral, grade II, 10 g.), using the following eluents: benzene–hexane (4:1), benzene, and benzene–ether (9:1). The earlier fractions of the benzene–hexane eluate afforded IX (0.034 g.) of m.p. 268–272° (acetone–hexane), and the latter eluents (mostly from benzene–ether) yielded an additional amount of compound X (0.045 g.). The analytical sample of IX possessed the following physical characteristics: m.p. 269–271°; λ_{max} 222.5 mμ (ε 10,700); 5.72, 5.83 (CO), 6.00 μ (broad, CO and C=N); n.m.r., τ 2.50 (d),[23] 4.20 (d, J = 10 c.p.s., proton at C-1 and C-2), 6.33 (CH_3O), 8.30, 9.12 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50. Found: C, 65.33; H, 6.71.

Compound X melted at 240–243° and exhibited the following physical properties: $[\alpha]_D$ +207.1° (*c* 0.39); λ_{max} 237.5 mμ (ε 12,890); 5.73, 5.86 (CO), 5.97 μ (broad, CO and C=N); n.m.r., τ 4.19 (proton at C-4), 6.34 (CH_3O), 8.40, 9.05 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50; N, 3.62;

(20) T. Kawasaki and E. Mosettig, *J. Org. Chem.*, **27**, 1374 (1962).

(21) Although thin layer chromatography of the product indicated homogeneity, a contaminant is probably responsible for the phenomenon. Correct analytical values for this compound could not be obtained (*Anal.* Calcd. for $C_{21}H_{31}O_4NS$: C, 64.09; H, 7.95. Found: C, 62.65, 62.36; H, 8.14, 8.18.). We believe that this is due to difficulties involved in removing the solvent from the compound since the infrared spectrum shows an absorption at 5.78 μ due probably to the ethyl acetate used in the precipitation.

(22) Prepared by adding in order: potassium thiocyanate (58.4 g.), water (30 ml.), glacial acetic acid (240 ml.), and 4 *N*-sulfuric acid (150 ml.) with ice cooling. The supernatant was used for the reaction (approximately equal to 1.43 *N* thiocyanic acid in 57% acetic acid).

(23) d, a doublet peak.

S, 8.27; CH_3O, 8.01. Found: C, 65.23; H, 6.77; N, 3.92; S, 8.5; CH_3O, 8.30.

The Catalytic Hydrogenation of IX into II (R = O).—A mixture of IX (0.010 g.) and 10% palladium–charcoal (0.005 g.) in ethyl acetate (5.0 ml.) was hydrogenated at room temperature under atmospheric pressure for 5 hr. The compound crystallized from methanol to afford prisms, melting at 226–228°. Its identity with II (R = O) was established by mixture melting point determination and comparison of their infrared spectra.

Acknowledgment.—The authors wish to express their great indebtedness to Dr. Edwin D. Becker of this institute for the interpretation of the n.m.r. spectra and to Mr. Robert B. Bradley for running the spectra. We wish also to thank the Cancer Chemotherapy National Service Center for the supply of valuable starting materials.

Investigations on Steroids. XXXV. Pseudostrophanthidin and Related Compounds[1,2]

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An improved method for the conversion of strophanthidin (I) into pseudostrophanthidin (II) is reported. Old and new evidence in support of the structure of II is discussed. In particular, II has been correlated with a number of steroids previously investigated in this laboratory. The earlier literature in this area has been reviewed and is presented in a revised form, *viz.*, in the light of present concepts. The structure of II appears now firmly established.

As a continuation of our studies on 19:8-lactone analogs of progesterone and cortexone[4] it appeared desirable also to prepare compounds of the 19:8-hemiacetal series. In an early investigation, Jacobs and Collins[5] had demonstrated that, by treatment with concentrated hydrochloric acid, strophanthidin (I) is converted into a crystalline isomer which was named pseudostrophanthidin. Its correct structure (II) was recognized by Fieser and Fieser,[6] and this interpretation is in agreement with our own investigations in this area.

Because of its structural features, pseudostrophanthidin (II) was considered as starting material for the synthesis of a variety of steroids with a 19:8-hemiacetal bridge. As the first task, it appeared necessary to repeat and consolidate some of the early experimental work. Furthermore, since it is cumbersome and sometimes confusing to excerpt and interpret data in the early literature, it was deemed advisable to arrange the pertinent findings in a revised form, *viz.*, in the light of present concepts.

Pseudostrophanthidin (II) was prepared in improved yield by a modified procedure. The deviations from the early literature[5] concerning the melting point and optical rotation are recorded in the Experimental section. Pseudostrophanthidin (II) was characterized by the preparation of several derivatives. Refluxing of II with methanol in the presence of a catalytic amount of hydrochloric acid gave pseudostrophanthidin methylal (III),[7] which could be reconverted into II by treatment with 70% acetic acid. The methylal (III) in turn was characterized as the dinitrobenzoate and acetate, *viz.*, pseudostrophanthidin methylal 3,5-dinitrobenzoate (IV) and pseudostrophanthidin methylal 3-acetate (V), respectively. On demethylating V, pseudostrophanthidin 3-monoacetate (VI) resulted which could be further acetylated at an elevated temperature, yielding pseudostrophanthidin 3,19-diacetate (VII). Acetylation of II at room temperature gave a mixture of the 3-monoacetate (VI) and the 3,19-diacetate (VII).

Pseudostrophanthidin (II) could be correlated with a number of compounds structurally connected with strophanthidinic acid lactone (X) which is prepared from strophanthidinic acid (IX).[8] X recently has served as a starting material for synthetic work in this laboratory.[4] In agreement with earlier observations,[8] oxidation with chromic acid of either II or X gave strophanthidonic acid lactone (XI). In addition, acetylation of X gave strophanthidinic acid 19:8-lactone 3-acetate (XII) which also was obtained by oxidation of VI with chromic acid. Another product belonging to this series is 3-dehydropseudostrophanthidin methylal (VIII) which resulted from the oxidation of III with chromic acid.

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) The findings reported in this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein," Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was presented by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961).

(5) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **63**, 123 (1925).

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 523–524; *cf.* also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 742–744.

(7) From a theoretical point of view, one may consider the existence of two epimeric forms in the series of the C-19 methyals. Only one form was isolated in the present instance.

(8) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **65**, 491 (1925).