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114. Taichiro Komeno: Bile Acids and Steroids. XVII.*2 Thiosteroids. (6). Synthesis of 16β-Mercapto-17α-hydroxyprogesterone and 16β-Mercaptotestosterone.

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In the preceding papers of this series,[1][*2] it was shown that steroidal epoxides in B- and C-ring could be opened by thiocyanic acid to give the corresponding thiocyanatohydrins. In the present paper, ring-opening reaction of a few 16α,17α-epoxides by thiocyanic acid is described.

16α,17α-Epoxy-4-androsten-3-one[2] (I) was treated with thiocyanic acid in ether solution and 16β-thiocyanato-17α-hydroxy-4-androsten-3-one (II), m.p. 190~192°, was obtained and its structure was assumed by Barton's generalization.[3] However, 3β-hydroxy-16α,17α-epoxy-5-pregnen-20-one[4] (IIIa) and its acetate (IIIb) were not affected by treatment with thiocyanic acid in ether solution or in chloroform solution. When the epoxide (IIIa) and its acetate (IIIb) were heated on a steam bath with potassium thiocyanate in acetic acid solution, a thiocyanatohydrin (IVa), m.p. 218~220°, and its 3-acetate (IVb), m.p. 208~210° (decomp.), were respectively isolated. Though (IVb) was pure, (IVa) was a mixture of 70% of pure (IVa) and 30% of the parent epoxide (IIIa) from the analytical data. Treatment of each substance with alkali gave the parent epoxide. The Oppenauer oxidation of the impure thiocyanatohydrin (IVa) gave an α,β-unsaturated ketone (V), m.p. 204~206°, not containing S or N atom, and it was established to be 16α,17α-epoxy-4-pregnene-3,20-dione, since it was also obtained by the Oppenauer oxidation of the parent epoxide (IIIa). This shows that the thiocyanatohydrin underwent ring closure to the epoxide by a basic reagent. When the compound (V) was similarly heated with potassium thiocyanate in acetic acid solution, the expected 16β-thiocyanato-17α-hydroxy-4-pregnene-3,20-dione (VI), m.p. 237~239° (decomp.), was obtained in a good yield. Ketalization of this compound was attempted by distillation[5] in the presence of *p*-toluenesulfonic acid and 3,3;20,20-bis(ethylenedioxy) compound (VII), m.p. 224~225° (decomp.), in which the thiocyanato group was not affected, was obtained. Reduction of the bis(ethylenedioxy) compound (VII) with lithium aluminium hydride, followed by heating with aqueous acetic acid, gave 16β-mercapto-17α-hydroxy-4-pregnene-3,20-dione (VIIIa), m.p. 172~174°, which showed a band at 2580 cm^{-1} in its infrared spectrum, presumably due to the mercapto group. Such a band has not yet been observed in a number of mercaptosteroids prepared by the author. Its acetylation with pyridine and acetic anhydride gave a monoacetate (VIIIb), m.p. 176~178°, which exhibited absorption bands due to the acetylthio group in its infrared and ultraviolet spectra.

Ellis and Petrow[6] reported that the Beckmann rearrangement of 16β-halo-17α-hydroxypregnenolone oxime 3-acetate with phosphoryl chloride and pyridine afforded 3β-hydroxy-16β-halo-5-androsten-17-one 3-acetate in a good yield. Thus, for the purpose of the above-mentioned rearrangement, thiocyanatohydrin oxime (IX) was pre-

*1 Imafuku, Amagasaki, Hyogo-ken (米野太一郎).
*2 Paxt XVI. T. Komeno: This Bulletin, 8, 672(1960).
1) K. Takeda, T. Komeno: *Ibid.*, 8, 468(1960).
2) H. Heusser, M. Feurer, V. Prelog: Helv. Chim. Acta, **33**, 2242(1950).
3) D. H. R. Barton: J. Chem. Soc., **1953**, 1027.
4) P. L. Julian, E. W. Meyer, W. J. Kappel, I. K. Wallen: J. Am. Chem. Soc., **72**, 5145(1950); B. Löken, S. Kaufmann, G. Rosenkranz, F. Sondheimer: *Ibid.*, **78**, 1738(1956).
5) W. S. Allen, S. Bernstein, R. Littell: *Ibid.*, **76**, 6116(1954).
6) B. Ellis, V. Petrow: J. Chem. Soc., **1958**, 800.

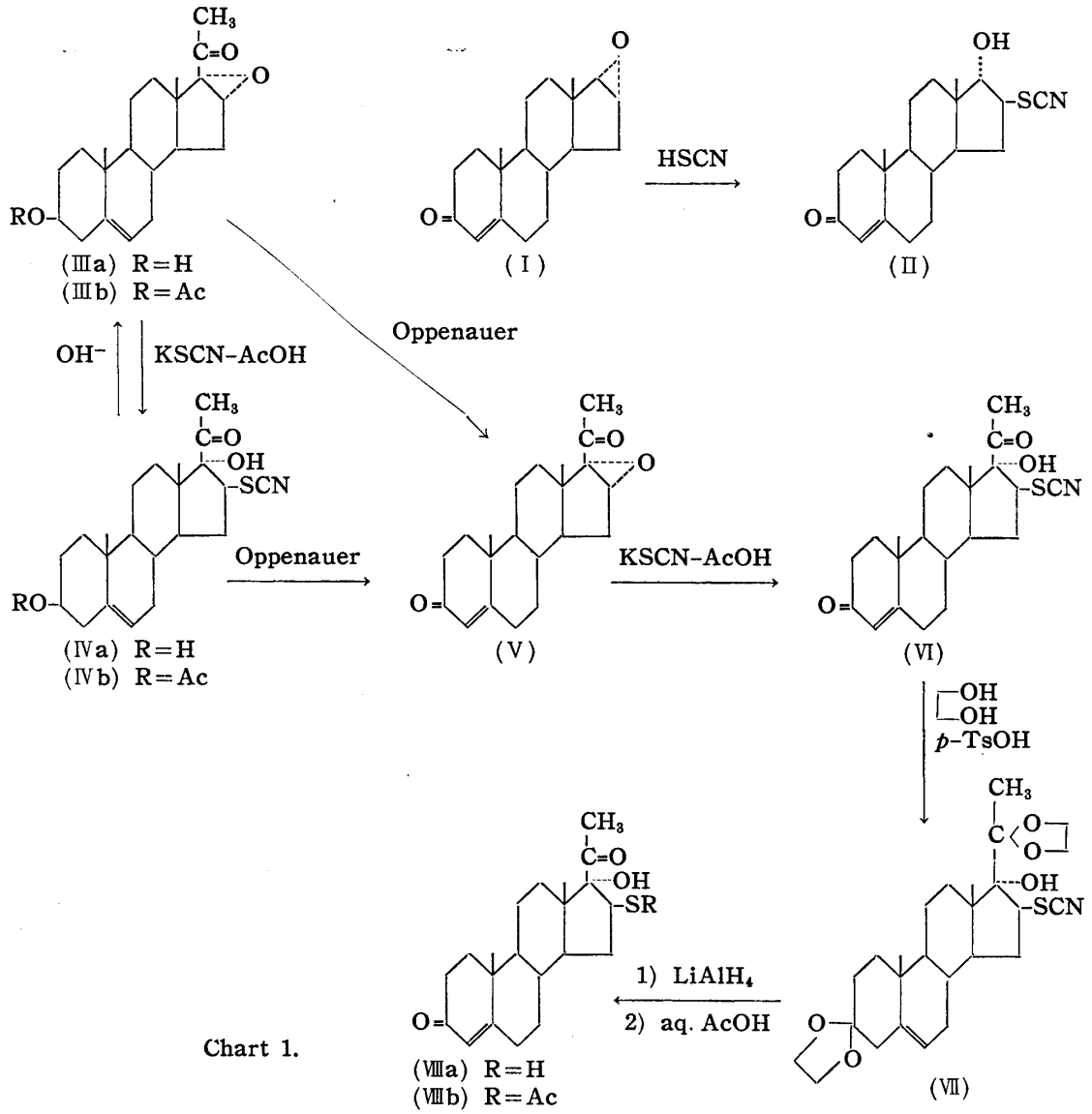

Chart 1.

pared by the usual method. However, the oxime (IX), m.p. 218~220° (decomp.), thus obtained did not show an absorption band due to the thiocyanato group but a band due to the C=N bond in its infrared spectrum. Hoggarth and Sexton[7] reported that aromatic thiocyanic esters could be converted in a good yield into disulfides via thiols by the action of tertiary amines and that the reaction was more complicated with side reactions when primary or secondary amines were used. In the case of the oxime (IX), it was assumed that such a reaction should occur in the presence of hydroxylamine and that the reaction product might be a mixture of a thiol oxime (IXa) and an oxime disulfide (IX). This assumption was confirmed by the establishment of structures for the Beckmann rearrangement products of (IX) as mentioned below. Treatment of the oxime (IX) with phosphoryl chloride in pyridine gave a normal rearrangement product (X), m.p.

7) E. Hoggarth, W. A. Sexton: J. Chem. Soc., **1947**, 815. They assumed that the mechanism would be as follows:

a) $RSCN + N\!\!\leftarrow \longrightarrow R\text{-}S\text{-}C(=\overline{N})\text{-}N\!\!\leftarrow$

b) $R\text{-}S\text{-}C(=\overline{N})\text{-}N\!\!\leftarrow + 2H_2O \longrightarrow RSH + CO_2 + NH_3 + N\!\!\leftarrow$

c) $RSH + RSCN \longrightarrow RSSR + HCN$

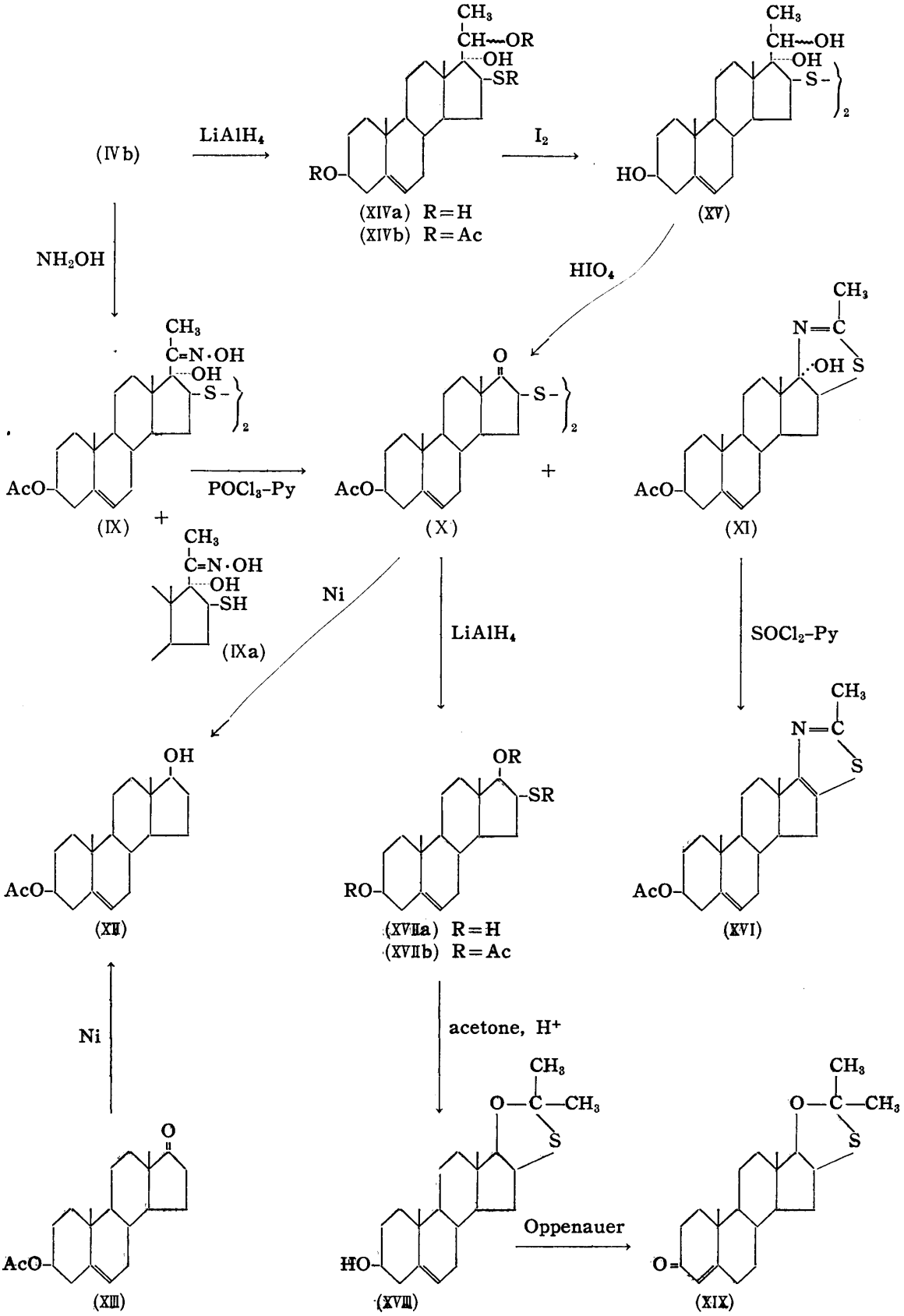

Chart 2.

258~260°(decomp.), in 26% yield and a by-product (XI), m.p. 254~255°(decomp.), in 16% yield. The compound (X), which showed an absorption maximum at 315 mμ in its ultraviolet spectrum, was proved to be 16β,16'β-dithio-bis(3β-acetoxy-5-androsten-17-one) from the following reactions. This compound was not affected by heating with pyridine-acetic anhydride and was reduced by Raney nickel to 5-androstene-3β,17β-diol 3-monoacetate (XII), which was identical with the reduction product of dehydroepiandrosterone 3-acetate (XIII) with the same reagent. On the other hand, reduction of the thiocyanatohydrin (IVb) with lithium aluminium hydride gave 16β-mercapto-5-pregnene-3β,17α,20ξ-triol (XIVa), m.p. 191~194°. Acetylation of (XIVa) with pyridine-acetic anhydride yielded a 3,16,20-triacetate (XIVb), m.p. 187~189°, and its ultraviolet and infrared spectra showed the absorption bands corresponding to the acetylthio group. Oxidation of the mercaptotriol (XIVa) with iodine in methanol gave a 16β-disulfide (XV), m.p. 280~282°(decomp.), and treatment of this disulfide with periodic acid, followed by acetylation, afforded the same compound as the previously obtained Beckmann rearrangement product (X). These results show that the structures of (IX) and (X) are correct. In this case, oxidative fission of the disulfide (XV) was attempted by sodium bismuthate or lead tetraacetate but was unsuccessful.

Analytical data of the by-product (XI) of the Beckmann rearrangement agree well with $C_{23}H_{33}O_3NS$ and its infrared spectrum exhibited a broad band due to a hydroxyl group (3483~3391 cm^{-1}) and a C=N bond (1604 cm^{-1}). Dehydration of this by-product (XI) with thionyl chloride in pyridine gave a basic compound (XVI), m.p. 133~135°, which showed a band in its infrared spectrum at 1507 cm^{-1} due to the aromatic ring and formed a picrate of m.p. 187~189°. In the Beckmann rearrangement of the oxime (IX), the sulfur anion presumably formed from the mercapto group would have two chances to attack the nitrogen cation in (A) stage, or carbon cation in (B) stage; in the former case the basic compound produced by dehydration would be an isothiazole derivative, while in the latter case it would be a thiazole derivative.

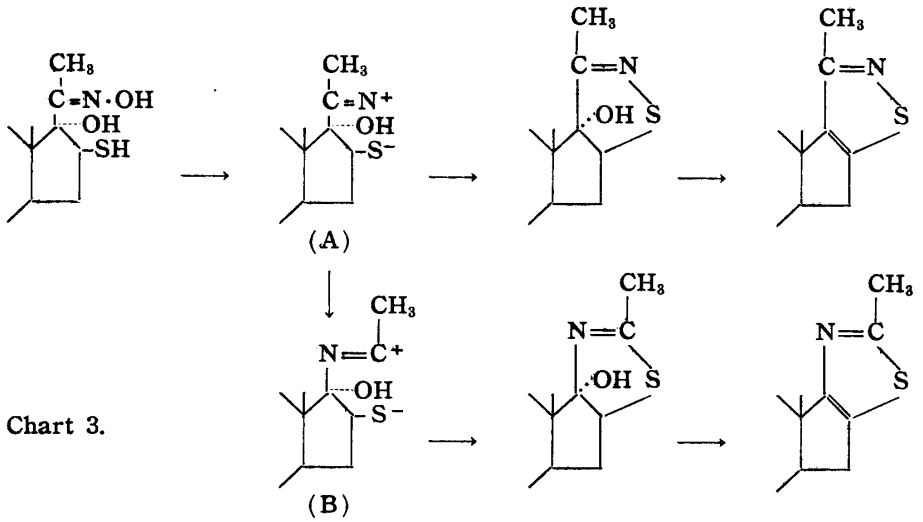

Chart 3.

However, a monocyclic isothiazole is unknown and a benzisothiazole is only known in the literature.[8] From this consideration it was assumed that the basic compound (XVI) would be 2'-methylthiazolo[5',4'-16,17]androsta-5,16-dien-3β-ol 3-acetate and consequently that the compound (XI) may be 2'-methyl-4',5'-dihydrothiazolo[5',4'-16,17]androst-5-ene-3β,17-diol 3-acetate.

8) L. Bambas: "Five-membered Heterocyclic Compounds" 225(1952). A monocyclic isothiazole was recently prepared by A. Adams and R. Slack (J. Chem. Soc., **1959**, 3061).

Synthesis of 16β-mercaptotestosterone was attempted and 16β,16'β-dithio bis(3β-acetoxy-5-androsten-17-one)(X) was used as the starting material. Reduction of the disulfide (X) with lithium aluminium hydride gave a crude product (XVIIa), which was purified by acetylation to give a triacetate (XVIIb), m.p. 200~222°, and it exhibited absorption bands due to the acetylthio group in both infrared and ultraviolet spectra. When the crude reduction product (XVIIb) was treated with sulfuric acid and acetone or with acetone in the presence of *p*-toluenesulfonic acid, 16β-mercapto-5-androstene-3β,17β-diol 16,17-acetonide (XVIII), m.p. 214~216°, was obtained, the *gem*-dimethyl group of this substance being identified by the infrared spectrum. The Oppenauer oxidation of (XVIII) gave the expected 16β-mercapto-17β-hydroxy-4-androsten-3-one 16,17-acetonide (XIX), m.p. 225~227°, and its structure was presumed from the spectral data. Attempts to obtain 16β-mercaptotestosterone from this compound (XIX) were unsuccessful.

Experimental*3

16β-Thiocyanato-17α-hydroxy-4-androsten-3-one (II)—A solution of 150 mg. of 16α,17α-epoxy-4-androsten-3-one (I), m.p. 190~195°(reported[2] m.p. 204~205°), in 20 cc. of HSCN-Et_2O solution was allowed to stand for 2 days at room temp. The reaction mixture was washed with H_2O, Na_2CO_3 solution, and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized twice from Me_2CO-hexane to 50 mg. of crystals (II), m.p. 190~192°. *Anal.* Calcd. for $C_{20}H_{27}O_2NS$: C, 69.53; H, 7.88; S, 9.28. Found: C, 69.21; H, 8.25; S, 8.83. IR ν_{max}^{Nujol} cm^{-1}: 3484(OH), 2155(SCN), 1658, 1613(4-en-3-one).

3β,17α-Dihydroxy-16β-thiocyanato-5-pregnen-20-one (IVa)—A solution of 2 g. of 3β-hydroxy-16α,17α-epoxy-5-pregnen-20-one (IIIa) and 8 g. of KSCN in 60 cc. of AcOH was heated on a steam bath for 5 hr., poured into H_2O, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, Na_2CO_3 solution, and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from Et_2O and recrystallized twice from Me_2CO to 1.2 g. of needles (IVa), m.p. 218~220°. *Anal.* Calcd. for (30% $C_{21}H_{30}O_3$+70% $C_{22}H_{31}O_3NS$): C, 70.38; H, 8.51: N, 2.52; S, 5.76. Found: C, 70.23; H, 8.43; N, 2.50; S, 5.93;. IR ν_{max}^{Nujol} cm^{-1}: 3587, 3562, 3302(OH), 2176(SCN), 1696(C=O).

3β,17α-Dihydroxy-16β-thiocyanato-5-pregnen-20-one 3-Acetate (IVb)—A solution of 5 g. of 3β-acetoxy-16α,17α-epoxy-5-pregnen-20-one (IIIb) and 20 g. of KSCN in 150 cc. of AcOH was heated on a steam bath for 6 hr., concentrated *in vacuo*, H_2O added, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed to neutrality, dried, and evaporated to dryness. The residue was crystallized from Et_2O to 3.5 g. of crystals (IVb), m.p. 180°/208~210°, and 0.4 g. of crystals, m.p. 160°/190°. Recrystallization from Me_2CO-hexane gave an analytically pure sample, m.p. 180°/208~210°. $[\alpha]_D^{26}$ +65.3° ±2°(c=1.066, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{33}O_4NS$: C, 66.79; H, 7.71; N, 3.25; S, 7.43. Found: C, 67.25; H, 7.85; N, 3.23; S, 7.43. IR ν_{max}^{Nujol} cm^{-1}: 3478(OH), 2152(SCN), 1735, 1241(OAc), 1711(C=O).

A solution of 200 mg. of this compound in 20 cc. of 5% KOH-MeOH was heated under reflux for 30 min. and H_2O added. The precipitate was collected by filtration, dried, and acetylated with 1 cc. of pyridine and 1 cc. of Ac_2O. The product was recrystallized from MeOH to 120 mg. of (IIIb), m.p. 156~160°, which was identified by mixed m.p. and the infrared spectrum.

16α,17α-Epoxy-4-pregnene-3,20-dione (V)—a) From (IIIa): A solution of 3 g. of (IIIa) in 75 cc. of toluene and 15 cc. of cyclohexanone was distilled to give 15 cc. of a distillate and then slow distillation was continued while a solution of 2 g. of Al(iso-PrO)$_3$ in 50 cc. of toluene was added dropwise over a period of 1 hr. After slow distillation for further 1 hr., the reaction mixture was treated as usual. The product was crystallized from Et_2O to 1.9 g. of needles. Chromatography of the mother liquor gave further 400 mg. of the same crystals. Recrystallization from Me_2CO-MeOH gave 2.10 g. of needles (V), m.p. 204~206°, $[\alpha]_D^{27}$ +164.3°±2°(c=1.047, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.13; H, 8.34. UV: λ_{max}^{EtOH} 241 mμ (ε 16,600), IR ν_{max}^{Nujol} cm^{-1}: 1700(C=O), 1669, 1606(4-en-3-one).

b) From (IVa): In 50 cc. of toluene, 500 mg. of (IVa) was treated with 5 cc. of cyclohexanone and a solution of 500 mg. of Al(iso-PrO)$_3$ in 15 cc. of toluene as described above. The product was chromatographed over Al_2O_3 to give 250 mg. of needles, m.p. 180~190°, from Et_2O-petr. ether, which

*3 All melting points determined in capillary tubes are uncorrected. Infrared spectra were measured with a Koken Infrared spectrophotometer, Model DS-301, and ultraviolet spectra were taken with a Beckmann Spectrophotometer, Model DU.

were recrystallized twice from MeOH to needles (V), m.p. 202~204°. This compound was identified with the above compound by mixed m.p. and infrared spectral comparison.

16β-Thiocyanato-17α-hydroxy-4-pregnene-3,20-dione (VI)—A solution of 2.279 g. of (V) and 9 g. of KSCN in 50 cc. of AcOH was heated on a steam bath for 5 hr. and treated as above. The product was crystallized from MeOH and recrystallized from $CHCl_3$-MeOH to 1.814 g. of needles (VI), m.p. 237~239° (decomp.). $[\alpha]_D^{31}$ +162.8°±4° (c=0.405, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{29}O_3NS$: C, 68.18; H, 7.54; N, 3.61; S, 8.27. Found: C, 68.18; H, 7.74; N, 3.49; S, 8.23. UV λ_{max}^{EtOH} 240 mμ (ε 17,700). IR ν_{max}^{Nujol} cm^{-1}: 3262 (OH), 2162 (SCN), 1703 (C=O), 1633, 1610 (4-en-3-one).

3,3 : 20,20-Bis(ethylenedioxy)-16β-thiocyanato-5-pregnen-17α-ol (VII)—A suspension of 1.68 g. of (VI) and 70 mg. of *p*-TsOH in 150 cc. of ethyleneglycol was distilled at 3~5 mm. Hg. After a slow distillation for 6 hr., H_2O was added to the reaction mixture. The precipitate formed was colleted by filtration and dried. The product was recrystallized from CH_2Cl_2-MeOH to 1.62 g. of needles (VII), m.p. 224~225° (decomp.). $[\alpha]_D^{29}$ +42.1°±3° (c=0.736, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{37}O_5NS$: C, 65.65; H, 7.84; N, 2.95; S, 6.74. Found: C, 65.81; H, 7.97; N, 3.33; S, 6.68. UV λ_{max}^{EtOH} 263 mμ (ε 92). IR ν_{max}^{Nujol} cm^{-1}: 3156 (OH), 2154 (SCN).

16β-Mercapto-17α-hydroxy-4-pregnene-3,20-dione (VIIIa)—A solution of 400 mg. of (VII) in 40 cc. of a mixture of dry tetrahydrofuran-Et_2O (1:1) was added dropwise with stirring into a suspension of 200 mg. of $LiAlH_4$ in 20 cc. of dry Et_2O. After refluxing for 1 hr., ice and dil. HCl were added to the reaction mixture and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, Na_2CO_3 solution, and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in 10 cc. of 80% AcOH and heated on a steam bath for 1 hr. The mixture was concentrated *in vacuo*, H_2O added, and extracted with $CHCl_3$-Et_2O (1:4). The organic solution was washed to neutrality, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed over 5 g. of Florisil. The eluate of benzene and benzene-$CHCl_3$ (9:1-1:1) (174 mg.) was crystallized from Et_2O to 126 mg. of needles, m.p. 170~173°, which were recrystallized twice from Me_2CO-hexane to needles (VIIIa), m.p. 172~174°. $[\alpha]_D^{29}$ +94.3°±3° (c=0.878, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34; S, 8.85. Found: C, 69.57; H, 8.37; S, 8.98. UV: λ_{max}^{EtOH} 241 mμ (ε 16,800). IR ν_{max}^{Nujol} cm^{-1}: 3348 (OH), 2580 (SH), 1710 (C=O), 1660, 1615 (4-en-3-one).

16β-Acetylthio-17α-hydroxy-4-pregnene-3,20-dione (VIIIb)—A solution of 60 mg. of (VIIIa) in 1 cc. of pyridine and 1 cc. of Ac_2O was allowed to stand overnight at room temp. and was treated as usual. The product was recrystallized twice from Me_2CO-hexane to give 40 mg. of prisms (VIIIb), m.p. 176~178°. $[\alpha]_D^{29.5}$ +87.1°±3° (c=0.897, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.93. Found: C, 68.41; H, 8.08; S, 7.52. UV: λ_{max}^{EtOH} 240 mμ (ε 10,400). IR ν_{max}^{Nujol} cm^{-1}: 3383 (OH), 1702 (sh. C=O), 1690, 1116 (S-Ac), 1641, 1604 (4-en-3-one).

Beckmann Rearrangement of (IVb)—To a hot solution of 3.5 g. of (IVb) in 50 cc. of EtOH, a solution of 3.0 g. of $NH_2OH \cdot HCl$ and 3.6 g. of NaOAc in 25 cc. of H_2O was added, heated on a steam bath until in complete solution, allowed to stand overnight at room temp., and then concentrated. The precipitate formed was collected by filtration, washed with 50% EtOH, and recrystallized from hydr. EtOH to 2.5 g. of silky needles (IX), m.p. 218~220° (decomp.). $[\alpha]_D^{27}$ −25.1°±4° (c=0.506, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{35}O_4NS \cdot \frac{1}{2}H_2O$: C, 64.15; H, 8.43; N, 3.25; S, 7.45. Calcd. for $(C_{23}H_{34}O_4NS)_2 \cdot H_2O$: C, 64.30; H, 8.21; N, 3.26; S, 7.46. Found: C, 63.79; H, 8.11; N, 3.59; S, 7.35. UV: λ_{max}^{EtOH} 281 mμ (ε 700). IR ν_{max}^{Nujol} cm^{-1}: 3409, 3321, 3239 (OH), 1732, 1707, 1274, 1242 (O-Ac), 1634 (C=N).

To a solution of 2.5 g. of (IX) in 11 cc. of pyridine, a solution of 1.8 cc. of $POCl_3$ and 5.4 cc. of pyridine was added dropwise over a period of 10 min. with stirring, and cooling with ice and NaCl. The reaction mixture colored and a precipitate appeared. After stirring with cooling for 2 hr., ice was added to the mixture and the precipitate was collected by filtration. The product was recrystallized from MeOH and further from Me_2CO to 450 mg. of leaflets (X), m.p. 258~260° (decomp.). $[\alpha]_D^{26}$ +83.6°±4° (c=0.578, dioxane). *Anal.* Calcd. for $(C_{21}H_{29}O_3S)_2$: C, 69.77; H, 8.09; S, 8.87. Found: C, 70.14; H, 8.18; S, 8.70. UV: $\lambda_{max}^{dioxane}$ 315 mμ (ε 470). IR ν_{max}^{Nujol} cm^{-1}: 1734, 1233 (O-Ac), 1743 (C=O). $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727, 1735 (sh).

The mother liquor (1.47 g.) was dissolved in benzene and chromatographed on Florisil. The eluate (498 mg.) with benzene and benzene-Et_2O (19:1-9:1) was recrystallized from MeOH to 365 mg. of needles (XI), m.p. 254~255° (decomp.). $[\alpha]_D^{31}$ −124.0°±3° (c=0.679, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{33}O_3NS$: C, 68.45; H, 8.24; N, 3.47; S, 7.95. Found: C, 68.81; H, 8.59; N, 3.66; S, 7.82. UV λ_{max}^{EtOH} mμ (ε): 255, 272 (sh) (3430, 2420). IR ν_{max}^{Nujol} cm^{-1}: 3483~3391 (OH), 1726, 1242 (O-Ac), 1604 (C=N).

The eluate (462 mg.) with benzene-EtOH (4:1-1:1) and Et_2O-$CHCl_3$ (1:1) was recrystallized from Me_2CO to further 100 mg. of (X), m.p. 255~258° (decomp.).

5-Androstene-3β,17β-diol 3-Monoacetate (XII)—a) From dehydroepiandrosterone acetate (XIII): To a solution of 200 mg. of (XIII) in 6 cc. of dioxane, 1 g. of Raney Ni was added, the mixture was heated on a steam bath for 8 hr., and Ni was filtered off. The filtrate was evaporated to dryness and the residue was recrystallized from hydr. MeOH to 110 mg. of plates (XII), m.p. 143~144°. $[\alpha]_D^{30}$ −63.4°±3°

(c=0.790, $CHCl_3$). (reported[9] m.p. 147~148°). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.71: Found: C, 75.93; H, 9.68. IR ν_{max}^{Nujol} cm^{-1}: 3450(OH), 1735, 1250(O-Ac).

b) From (X): A suspension of 70 mg. of (X) and 1 g. of Raney Ni in 6 cc. of dioxane was heated for 8 hr. and treated as above. The product was recrystallized from hydr. MeOH to 50 mg. of plates, m.p. 137~139°, mixed m.p. 142~144° with the above cited compound (XII). Its infrared spectrum was in full agreement with that of (XII).

16β-Mercapto-5-pregnene-3β,17α,20ξ-triol (XIVa)—A solution of 3.0 g. of (IVb) in a mixture of 50 cc. of tetrahydrofuran and 20 cc. of anhyd. Et_2O was added with stirring into a suspension of 800 mg. of $LiAlH_4$ in 70 cc. of anhyd. Et_2O over a period of 20 min. After agitation for 10 min., the mixture was heated under reflux for 1 hr., ice and dil. HCl were added, and extracted with Et_2O-$CHCl_3$ (4:1). After the organic solution was treated as usual, the product was crystallized from Et_2O and recrystallized from hydr. MeOH to 1.70 g. of crystals, m.p. 185~190°. which were further recrystallized from Me_2CO and from AcOEt to give 1.27 g. of crystals (XIVa), m.p. 191~194°. *Anal.* Calcd. for for $C_{21}H_{34}O_3S \cdot \frac{1}{2}C_4H_8O_2$: C, 67.28, H, 9.33; S, 7.81. Found: C, 67.30; H, 9.50; S, 7.47.

Acetylation of the mother liquor (1.20 g.) with pyridine-Ac_2O gave 1.45 g. of a product, which was chromatographed over 40 g. of Florisil. The oily product (240 mg.) eluated with benzene-Et_2O (99:1) was not studied further. The eluate (680 mg.) of benzene-Et_2O (49:1-9:1) was crystallized from Et_2O, and recrystallized from hydr. MeOH to 450 mg. of needles (XIVb), m.p. 187~189°. $[\alpha]_D^{31}$ −21.4°±2°(c=1.040, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{40}O_6S$: C, 65.82; H, 8.18; S, 6.51. Found: C, 65.57; H, 8.11; S, 6.38. UV: λ_{max}^{EtOH} 234 mμ (ε 5,360). IR ν_{max}^{Nujol} cm^{-1}: 3472(OH), 1734, 1702, 1274, 1231(O-Ac), 1702, 1141(S-Ac).

16β,16β'-Dithio-bis(5-pregnene-3β,17α,20ξ-triol) (XV)—To a solution of 720 mg. of (XIVa) in 10 cc. of MeOH, 250 mg. of I_2 was added with stirring at room temp. The reaction mixture slowly decolorized and crystals appeared. After agitation for 1 hr., the product was collected by filtration and washed with MeOH. It was further recrystallized from $CHCl_3$-MeOH to 590 mg. of crystals (XV), m.p. 280~282°(decomp.). *Anal.* Calcd. for $(C_{21}H_{33}O_3S)_2 \cdot 2CH_4O$: C, 66.46; H, 9.38; S, 8.06. Found: C, 66.75; H, 9.18; S, 8.48.

HIO_4 Oxidation of (XV)—To a solution of 330 mg. of (XV) in 15 cc. of dioxane, a solution of 530 mg. of HIO_4 in 0.5 cc. of H_2O was added and the mixture was agitated at room temp. for 2 hr. To the mixture H_2O was added and filtered. The product from acetylation with pyridine-Ac_2O was recrystallized from $CHCl_3$-MeOH to 100 mg. of crystals (X), m.p. 255~258°(decomp.), which was identified to be the same with the compound, m.p. 258~260°(decomp.), obtained by the Beckmann rearrangement since the mixed m.p. determination showed no depression and their infrared spectra in Nujol were in full agreement.

2'-Methylthiazolo[5',4'-16,17]androsta-5,16-dien-3β-ol 3-Acetate (XVI)—To a solution of 180 mg. of (XI), 0.2 cc. of $SOCl_2$ was added with cooling. The reaction mixture was allowed to stand for 1 hr. at room temp., ice and H_2O were added, and extracted with Et_2O. When Et_2O solution was washed with dil. HCl, the hydrochloride appeared. The turbid Et_2O solution was washed with NaOH solution and evaporated to dryness. The residue was recrystallized from hydr. MeOH to 150 mg. of needles, m.p. 128~133°, which were further recrystallized from a small amount of MeOH to plates (XVI), m.p. 133~135°. $[\alpha]_D^{29}$ −72.7°±2°(c=0.925, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{31}O_2NS$: C, 71.65; H, 8.10; N, 3.63; S, 8.32. Found: C, 71.62; H, 8.18; N, 3.39; S, 8.25. UV: λ_{max}^{EtOH} 254 mμ (ε 5,740). IR ν_{max}^{Nujol} cm^{-1}: 1731, 1242(sh), 1230(O-Ac), 1671(C=N), 1507(aromatic).

This compound formed a picrate in Et_2O, which was recrystallized from MeOH to needles, m.p. 187~189°. *Anal.* Calcd. for $C_{23}H_{31}O_2NS \cdot C_6H_3O_7N_3$: C, 56.67; H, 5.58; N, 9.12. Found: C, 56.36; H, 5.58; N, 8.96.

16β-Mercapto-5-androstene-3β,17β-diol 3,16,17-Triacetate (XVIIb)—The disulfide (X) (100 mg.) was reduced with 60 mg. of $LiAlH_4$ in 10 cc. of tetrahydrofuran and 10 cc. of dehyd. Et_2O in the same manner as cited above. The product was acetylated with pyridine and Ac_2O overnight at room temp. and recrystallized from Me_2CO-MeOH to 30 mg. of crystals (XVIIb), m.p. 220~222°. *Anal.* Calcd. for $C_{25}H_{36}O_5S$: C, 66.93; H, 8.09; S, 7.15. Found: C, 67.11; H, 7.99 S, 6.91. UV: λ_{max}^{EtOH} 233 mμ (ε 5,210). IR ν_{max}^{Nujol} cm^{-1}: 1743, 1728, 1250, 1230(O-Ac). 1689, 1139(S-Ac).

16β-Mercapto-5-androstene-3β,17β-diol 16,17-Acetonide (XVIII)—The disulfide (X) (2.722 g.) was reduced with 1.43 g. of $LiAlH_4$ in a mixture of 160 cc. of tetrahydrofuran and 80 cc. of anhyd. Et_2O for 1.5 hr. in the same manner as above. The crude (XVIIa) (2.415 g.) dissolved with 270 mg. of *p*-TsOH in 100 cc. of Me_2CO was heated under reflux for 8 hr. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from Me_2CO and further recrystallized from $CHCl_3$-MeOH to 1.259 g. of plates (XVIII), m.p. 214~216°. $[\alpha]_D^{29.5}$ −90.7°±3°(c=0.795, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{34}O_2S$: C, 72.88; H, 9.45; S, 8.84. Found: C, 73.11; H, 9.55;

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S, 8.78. IR ν_{max}^{Nujol} cm^{-1} : 3380 (OH), 1376, 1364 (CMe_2).

The crude (XVIIa) (549 mg.) dissolved in a mixture of 30 cc. of Me_2CO and 0.3 cc. of conc. H_2SO_4 was allowed to stand overnight at room temp. and treated as above. The product was recrystallized from $CHCl_3$–MeOH to 270 mg. of (XVIII).

16β-Mercapto-17β-hydroxy-4-androsten-3-one 16,17-Acetonide (XIX)—The above acetonide (XVIII) (90 mg.) dissolved in a mixture of 10 cc. of toluene and 1 cc. of cyclohexanone was added to 200 mg. of Al(iso-PrO)$_3$. The mixture was heated under reflux for 8 hr., and treated as usual. The product was chromatographed over 3 g. of Al_2O_3. The eluate of petr. ether–benzene (1:1) and benzene was crystallized from MeOH to 40 mg. of leaflets, m.p. 219~224°, and was further recrystallized from MeOH to leaflets (XIX), m.p. 225~227°. $[\alpha]_D^{29.5}$ +87.1°±3° (c=0.897, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.89. Found : C, 73.16; H, 9.00; S, 9.01. UV: λ_{max}^{EtOH} 241 mμ (ε 16,740). IR ν_{max}^{Nujol} cm^{-1} : 1680, 1616 (4-en-3-one), 1379, 1366 (C-Me_2).

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Summary

Some 16α,17α-epoxy-steroids were converted to the corresponding thiocyanato-hydrins, (II), (IVa), (IVb), and (VI). Oxime-formation reaction of 3β,17α-dihydroxy-16β-thiocyanato-5-pregnen-20-one 3-acetate (IVb) yielded a mixture of the oxime-thiol (IXa) and the oxime-disulfide (IX). These structures were assumed by identification of the Beckmann rearrangement products, (X) and (XI). Dehydration of the Beckmann rearrangement by-product (XI) gave a base (XVI), which was assumed to be 2′-methylthiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol 3-acetate from the consideration of the mechanism of the Beckmann rearrangement. From the normal product (X), 16β-mercapto-17β-hydroxy-4-androsten-3-one 16,17-acetonide (XIX) was synthesized in three steps.

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