UDC 547.92:547.931

113. Taichiro Komeno: Bile Acids and Steroids. XVI.*2 Thiosteroids. (5). Ring-opening Reaction of Steroidal 5α,6α- and 5β,6β-Epoxide by Thiocyanic Acid.

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In Part XII (1) of this series,[1] it was shown that treatment of steroidal epoxides in C-ring with thiocyanic acid gave corresponding thiocyanato-hydrins. The present paper describes the results obtained by this procedure applied to cholesterol β-epoxide and α-epoxide.

When 5β,6β-epoxycoprostan-3β-ol acetate (I) was treated with thiocyanic acid, as described in Part I, a thiocyanatohydrin*3 (II), m.p. 157~158°, was obtained, which was esterified to a thiocyanato-mesylate (III), m.p. 126~127°, with pyridine and mesyl chloride in a good yield. From this result it was assumed that the newly formed hydroxyl group in the compound (II) was situated at C-6 and this compound might be 5α-thiocyanato-cholestane-3β,6β-diol 3-acetate, agreeing with Barton's generalization.[2] As described in Part (3)[3] of this series, treatment of the thiocyanato-mesylate (III) with alkali gave a compound (IVa), m.p. 149~150°, having a sulfur atom, which was assumed to be 5α,6α-epithiocholestan-3β-ol from consideration of the reaction mechanism. By acetylation with pyridine and acetic anhydride, this compound (IVa) gave an acetate (IVb), m.p. 120~121°, which exhibited an absorption maximum at 264 mμ (ε 56) in its ultraviolet spectrum. Ultraviolet data of steroidal episulfides prepared up to the present are summarized in Table I. These values cited in Table I agree well with those observed for simple alkene sulfides by Evans[4] (λ_{max}^{EtOH} 261~263 mμ (log ε 34~39)).

Table I. Ultraviolet Data of Steroidal Episulfides

	λ_{max} (mμ)	ε
Methyl 3α-acetoxy-11β,12β-epithiocholanate	250*	50
11β,12β-Epithiocholane-3α,24-diol	257	61
5α,6α-Epithiocholestan-3β-ol acetate	264	56

* shoulder

5α,6α-Epithiocholestan-3β-ol (IVa) so obtained was reduced to a mercapto-ol with lithium aluminium hydride, yielding a considerable amount of a desulfurization product (cholesterol), and this result seems to differ from that of the 11β,12β-episulfide. When the 5α,6α-episulfide (IVa) was reduced with lithium aluminium hydride in boiling ether or in a mixture of ether and tetrahydrofuran at room temperature, cholesterol was obtained in nearly 40% yield, accompanied with a very small amount of the mercapto-ol. When the 5α,6α-episulfide (IVa) was reduced with the same reagent in a boiling mixture of ether and tetrahydrofuran, followed by acetylation, cholesteryl acetate in 40% yield and the compound (V), m.p. 142~143°, in 35% yield, were isolated. This compound (V)

*1 Imafuku, Amagasaki, Hyogo-ken (米野太一郎).

*2 Part XV. T. Komeno: This Bulletin, 8, 668(1960).

*3 This compound was analytically pure but not spectrally pure because absorption bands due to the isothiocyanato group were observed with that of the thiocyanato group in the infrared spectrum of this compound, but its mesylate, prepared in a good yield from this compound, exhibited only the absorption band due to thiocyanato group in its infrared spectrum.

1) K. Takeda, T. Komeno: This Bulletin, 8, 468(1960).
2) D. H. R. Barton: J. Chem. Soc., **1953**, 1027.
3) K. Takeda, T. Komeno, J. Kawanami: This Bulletin, 8, 621(1960).
4) R. E. Evans: J. Org. Chem., **23**, 216(1958).

was also obtained in 35% yield by reduction of the thiocyanato-mesylate (III) with the same reagent in boiling ether, followed by acetylation. This compound (V) showed an absorption maximum at 237 mμ in its ultraviolet spectrum and absorption bands at 1675 and 1114 cm^{-1} in its infrared spectrum, which are observed for both simple and steroidal thiol esters.[5] The results of lithium aluminium hydride reduction of these thiol derivatives are summarized in Table II.

Table II. $LiAlH_4$ Reduction of the Episulfide (IVa) and Thiocyanatomesylate (III)

Starting material	Conditions	Yield of reduction products* (%)		
		Cholesteryl acetate	Recovered 5α,6α-epi-sulfide(IVb)	5α-Mercapto-3β-ol di-acetate(V)
5α,6α-Epithiocholestan-3β-ol (IVa)	In boiling Et_2O	36	53	1
〃	In Et_2O and 4H-furan	37	51	1
〃	In boiling Et_2O and 4H-furan	39	7	35
3β-Acetoxy-5α-thiocyanato-6β-mesyloxycholestane (III)	In boiling Et_2O	39	8	35

* Reduction products were acetylated and then separated by chromatography over alumina.

From the consideration of data in Table II, it appears that the reduction of thiocyanato-mesylate (II) with lithium aluminium hydride does not proceed via the 5α,6α-episulfide and the mercapto group may therefore be present at C-5.

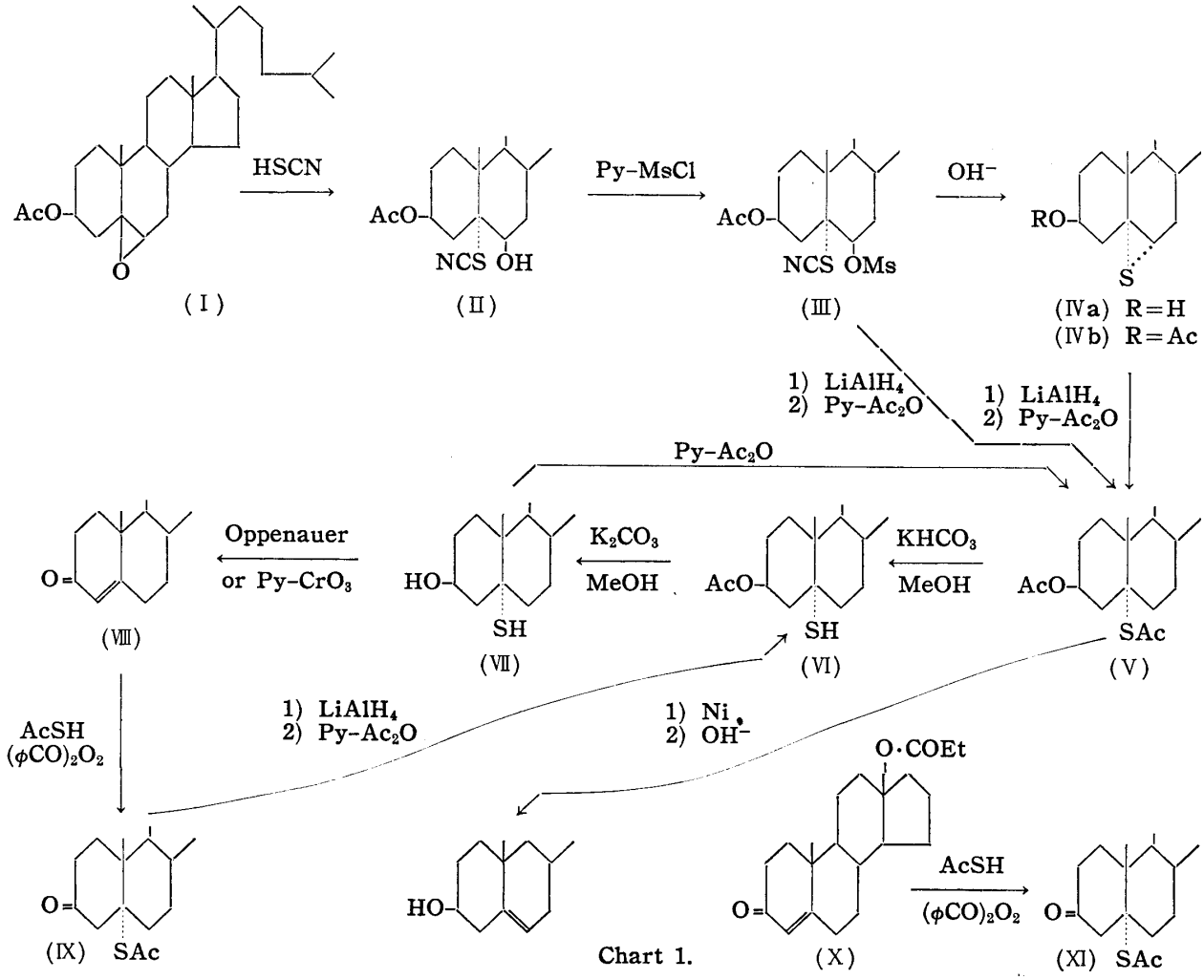

Chart 1.

5) L. H. Noda, S. A. Kuby, H. A. Lardy : J. Am. Chem. Soc., **75**, 913(1953); B. Sjöberg : Z. physik. Chem., **52B**, 209(1942); C. Djerassi, A. L. Nussbaum : J. Am. Chem. Soc., **75**, 3700(1953).

The compound (V) was desulfurized to cholesterol with Raney nickel. Saponification of the compound (V) with potassium hydrogencarbonate–methanol gave two compounds, (VI) of m.p. 167~169° in 61% yield and (VII) of m.p. 168~170° in 37% yield, while saponification with potassium carbonate–methanol gave the former in 11% yield and the latter in 84% yield. The former (VI) exhibited only the absorption bands due to O-acetate in its infrared spectrum, but the latter (VII) showed neither absorption bands due to the O-acetate nor the acetylthio group in both infrared and ultraviolet spectra. The compound (VI) or (VII) was regenerated to the parent diacetate (V) on heating with pyridine–acetic anhydride. Further, 4-cholesten-3-one (VIII) was obtained from (VII) by oxidation with pyridine–chromium trioxide complex or in a better yield by Oppenauer oxidation. The results show that the acetylthio group is at first saponified in the saponification of mercapto-ol diacetate (V).

On the other hand, Dodson[6] reported that by addition of thiolacetic acid, 1,4-dien-3-ones or 4,6-dien-3-ones were converted to 1α-acetylthio-4-en-3-ones or 7α-acetylthio-4-en-3-ones, respectively. However, the addition reaction of thiolacetic acid to 4-en-3-ones has not been reported. Addition reaction of thiolacetic acid to 4-cholesten-3-one was attempted in the presence of benzoyl peroxide and the compound (IX), m.p. 180~182°, was obtained in a low yield, which exhibited absorption bands due to the acetylthio group in its ultraviolet and infrared spectra. This compound was assumed to be 5α-acetylthiocholestan-3-one, because the approach of the reagent is possible only from the rear side of the molecule. Similarly, testosterone propionate (X) gave an analogous adduct (XI), m.p. 194~196°, by addition of thiolacetic acid and in this case transesterification of the 17-propionate to 17-acetate was not recognized.

When 5α-acetylthiocholestan-3-one (IX) was reduced with lithium aluminium hydride in ether and then acetylated with pyridine–acetic anhydride at room temperature overnight, a compound of m.p. 167~169° was obtained, which was identified with the compound (VI) obtained by partial saponification of the diacetate (V), by mixed melting point and the infrared spectrum.

From these chemical conversions, the diacetate (V), obtained by reduction of the episulfide, followed by acetylation, was assumed to be 5α-mercaptocholestan-3β-ol 3,5-diacetate.

Then it was also found that acetylation of 5α-mercapto-3β-ol and saponification of the diacetate (V) proceed as shown in Chart 2 and are quite different from those of

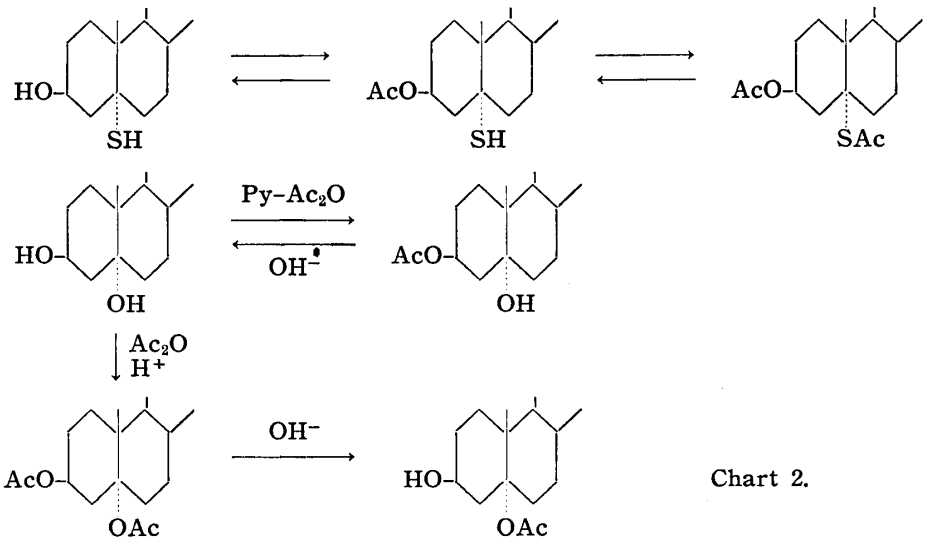

Chart 2.

6) R. M. Dodson, R. C. Tweit : J. Am. Chem. Soc., **81**, 1224(1959).

the corresponding 3β,5α-diol.[7]

The molecular rotation difference of 5α-mercapto-3β-ol derivatives also supports these assumptions (Table III).

Table III. Molecular Rotation Difference

	M_D		ΔSH		ΔSAc
5α-Mercaptocholestan-3β-ol diacetate (V)	+ 79			V-B	+22
5α-Mercaptocholestan-3β-ol 3-acetate (VI)	+ 2	VI-B	−55		
5α-Mercaptocholestan-3β-ol (VII)	+ 58	VII-A	−75		
Cholestan-3β-ol (A)	+133				
Cholestan-3β-ol acetate (B)	+ 57				
			5α-OH		5α-OAc
3β,5α-Diol*			−12		+49

* W. Klyne, D. H. R. Barton : Chem. & Ind. (London), **1948**, 755.

When 5α,6α-epoxycholestan-3β-ol (XII) was treated with thiocyanic acid similarly, a thiocyanato-hydrin (XIII), m.p. 184~185°, was obtained, which was converted by oxidation with chromium trioxide to an oxo-thiocyanato-hydrin (XIV), m.p. 181~182°, and the compound (XIII) formed a thiocyanato-diol monoacetate (XV), m.p. 132~133°, by acetylation with pyridine-acetic anhydride. The compound (XV) was also obtained by treatment of 5α,6α-epoxycholestan-3β-ol acetate (XVI) with thiocyanic acid. From these results it appears that the newly formed hydroxyl group by the ring-opening reaction of the 5α,6α-epoxide may be situated at C-5 and the product may be 6β-thiocyanato-3β,5α-diol derivative.

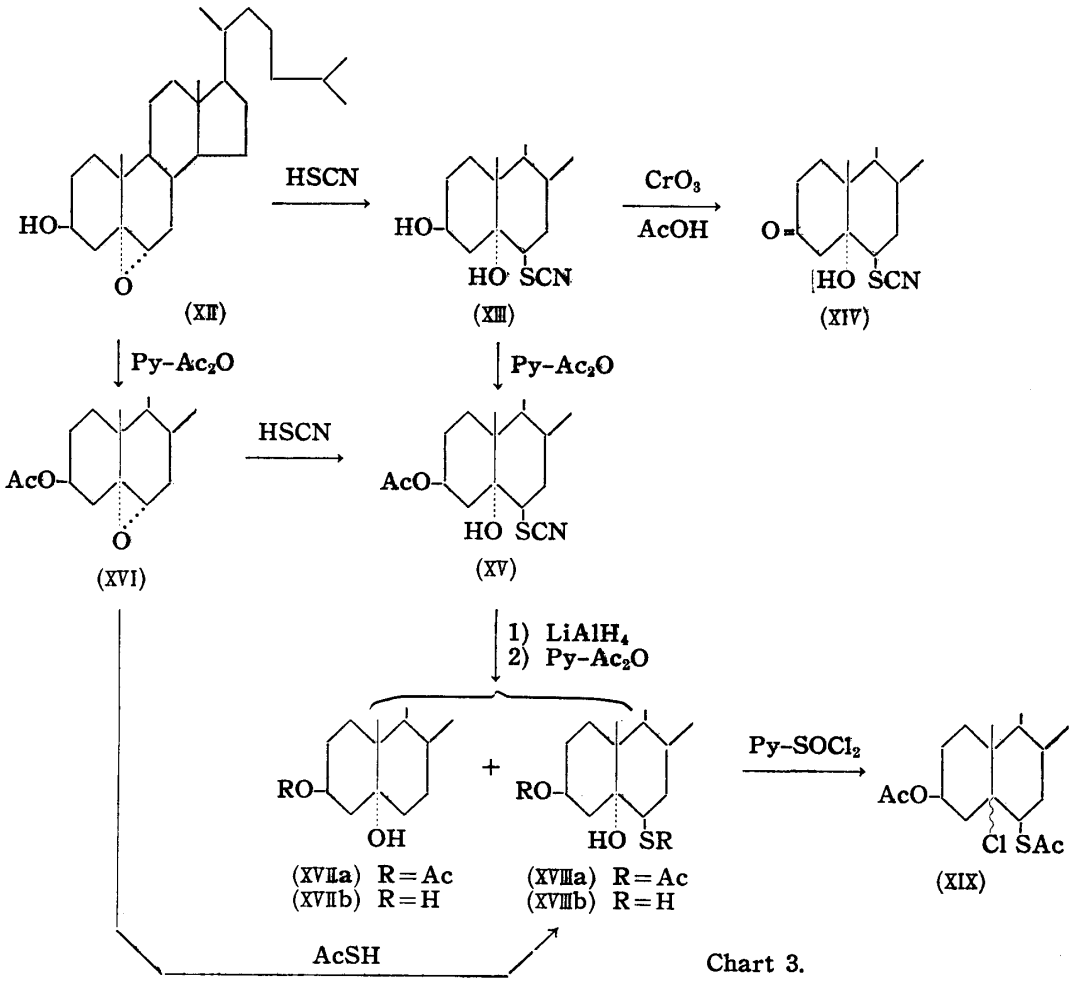

Chart 3.

7) L. F. Fieser, M. Fieser : "Natural Products related to Phenanthrene," 3rd Ed., 223.

By reduction of this compound (XIV or XV) with lithium aluminium hydride in ether, followed by acetylation, the known cholestane-3β,5α-diol 3-acetate (XVIIa), m.p. 183~185°, and the compound (XVIIIa), m.p. 134~136°, were isolated. The structure of (XVIIIa) was assumed to be 6β-mercaptocholestane-3β,5α-diol 3,6-diacetate from the fact that the compound (XVIII) exhibits absorption bands corresponding to acetylthio group in its ultraviolet and infrared spectra, and that this compound was also obtained by the fission of the 5α,6α-epoxide ring with thiolacetic acid. Saponification of this diacetate with alkali gave the expected mercapto-diol (XVIIIb), m.p. 188~190°, and a small amount of cholesterol. In this case, ring-closure of this *trans* diaxial mercapto-alcohol (XVIIIb) to the episulfide was not recognized, for the compound (XVIIIb) was regenerated to the parent diacetate (XIIIa) by acetylation. Though attempt was made to dehydrate the diacetate (XVIIIa) with pyridine and thionyl chloride, a dehydration product was not isolated and only a small amount of chlorine-containing compound (XIX), m.p. 161~162°, was the sole product isolated as crystals.

Experimental*4

5α-Thiocyanatocholestane-3β,6β-diol 3-Acetate (II)—A solution of 830 mg. of 5β,6β-epoxycoprostan-3β-ol acetate (I) (m.p. 114~115°, $[\alpha]_D$ +0.6° (c=2.8, $CHCl_3$)) (reported[8] m.p. 113~114°, $[\alpha]_D$ −0.5°) in 30 cc. of HSCN-Et_2O solution was allowed to stand for 2 days at room temp., washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from MeOH to 600 mg. of crystals, which were further recrystallized from MeOH to thin plates (II), m.p. 157~158°; $[\alpha]_D^{24}$ −38°±2° (c=0.796, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{49}O_3NS$: C, 71.52; H, 9.80; N, 2.78; S, 6.36. Found: C, 71.84; H, 9.95; N, 2.68; S, 6.23. IR ν_{max}^{Nujol} cm^{-1}: 3448 (OH), 2160 (SCN), 2128 (sh.), 2075, 2049 (sh.) (-N=C=S), 1739, 1704, 1269, 1258 (OAc).

3β-Acetoxy-5α-thiocyanato-6β-mesyloxycholestane (III)—To a solution of 2.00 g. of (II) in 20 cc. of pyridine, 2 cc. of mesyl chloride was added with cooling. The mixture was stored in a refrigerator overnight and extracted with Et_2O. Et_2O solution was washed to neutrality, dried over Na_2SO_4, and evaporated. The residue was crystallized from petr. ether to 1.80 g. of crystals, which were recrystallized from Et_2O-petr. ether to long plates (III), m.p. 126~127° (decomp.). $[\alpha]_D^{22}$ −70°±2° (c=0.720, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{51}O_5NS_2$: C, 63.99; H, 8.83; S, 11.02. Found: C, 63.84; H, 9.06; S, 10.89. IR ν_{max}^{Nujol} cm^{-1}: 2160 (SCN), 1736, 1242 (O-Ac), 1351, 1178 (OMs).

5α,6α-Epithiocholestan-3β-ol (IVa)—A solution of 600 mg. of (III) in 5 cc. of Et_2O was added to 40 cc. of boiling 3% KOH-MeOH, heated under reflux for 30 min., and H_2O was added. The precipitate was collected by filtration, dried, and recrystallized from acetone-MeOH to 400 mg. of needles (IVa), m.p. 149~150°. $[\alpha]_D^{24}$ −18°±2° (c=0.990, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{46}OS$: C, 77.45; H, 11.07; S, 7.66. Found: C, 77.34; H, 11.40; S, 7.39.

5α,6α-Epithiocholestan-3β-ol Acetate (IVb)—The above substance (IVa) was acetylated with pyridine-Ac_2O at room temp. overnight and the product was recrystallized from MeOH to needles (IVb), m.p. 120~121°. $[\alpha]_D^{24}$ −39°±2° (c=0.980, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.96. Found: C, 75.69; H, 10.69; S, 6.93. UV λ_{max}^{EtOH} mμ (ε): 207 (1,490), 264 (56). IR ν_{max}^{Nujol} cm^{-1}: 1733, 1241 (CAc).

5α-Mercaptocholestan-3β-ol 3,5-Diacetate (V)—a) From the episulfide (IVa): A solution of 680 mg. of (IVa) in 40 cc. of tetrahydrofuran was added dropwise with stirring into a suspension of 200 mg. of $LiAlH_4$ in 40 cc. of dehyd. Et_2O over a period of 30 min. and then heated under reflux for 1.5 hr. Ice and dil. HCl were added to destroy the excess reagent. Et_2O solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was heated on a steam bath with 4 cc. of pyridine and 4 cc. of Ac_2O for 2 hr. and then treated as usual.

The residue (800 mg.) was chromatographed over 24 g. of Al_2O_3. From the eluate with petr. ether, 270 mg. of cholesteryl acetate, m.p. 116~117°, was obtained (38.8% yield). From the eluate with petr. ether-benzene (49:1-19:1) 50 mg. of the episulfide acetate (IVb), m.p. 118~120°, was recovered (6.7% yield). The residue from the petr. ether-benzene (9:1-1:1) eluate was recrystallized from hydr. Me_2CO to 290 mg. of leaflets (V), m.p. 142~143° (35.4% yield.) $[\alpha]_D^{23}$ +15.7°±2° (c=1.146,

*4 All m.p.s were determined in capillary tube and are not corrected. Infrared spectra were measured with a Kôken Infrared Spectrophotometer, Model DS-301, and ultraviolet spectra were taken with a Beckman sepectrophotometer, Model DU.

8) J. Hattori: Yakugaku Zasshi, **60**, 334(1940); Pl. A. Plattner: Helv. Chim. Acta, **27**, 513(1944).

$CHCl_3$). *Anal.* Calcd. for $C_{31}H_{52}O_3S$: C, 73.76; H, 10.38; S, 6.35. Found : C, 73.57; H, 10.66; S, 6.23. UV : λ_{max}^{EtOH} 237 mμ (ε 5,770). IR ν_{max}^{Nujol} cm^{-1} : 1732, 1241 (O-Ac), 1675, 1114 (S-Ac).

The episulfide (IVa) (500 mg.) was reduced with 120 mg. of $LiAlH_4$ in 50 cc. of dehyd. Et_2O under reflux for 2 hr. and treated as above. By chromatography, 185 mg. of cholesteryl acetate (36.1%), 290 mg. of the episulfide (IVb) (52.7%), and 10 mg. of (V) were isolated.

The episulfide (IVa) (500 mg.) was reduced with 120 mg. of $LiAlH_4$ in a mixture of 20 cc. of tetrahydrofuran and 20 cc. of dehyd. Et_2O at room temp. and treated as above. By similar chromatography, 190 mg. of cholesteryl acetate (37.2%), 280 mg. of the episufide (IVa) (51.0%), and 10 mg. of (V) were isolated.

b) From (III) : The thiocyanato-mesylate (III) (1.54 g.) was reduced with 600 mg. of $LiAlH_4$ in 120 cc. of Et_2O under reflux for 2 hr. and treated as above. By chromatography, 440 mg. of cholesteryl acetate (38.8%), 90 mg. of the episulfide (IVb), and 470 mg. of (V) were isolated. In another run, 3.50 g. of (III) was reduced with 1.4 g. of $LiAlH_4$ in Et_2O, followed by acetylation, and gave 620 mg. of cholesteryl acetate (24.4%), 510 mg. of the episulfide (IVb), and 1.05 g. of (V) (35.2%). Identification was confirmed in each case by mixed m.p. and infrared spectral examination.

Saponification of 5α-mercaptocholestan-3β-ol 3,5-Diacetate (V)—a) With $KHCO_3$: A solution of 450 mg. of (V) and 520 mg. of $KHCO_3$ in 40 cc. of MeOH-EtOH (2:1) and 2 cc. of H_2O was heated under reflux for 15 min., when the precipitate appeared. After further refluxing for 30 min., the mixture was added to H_2O and extracted with Et_2O. Et_2O residue was chromatographed over 18 g. of Florisil. From the eluate with petr. ether-benzene (9:1-2:1), 250 mg. of 5α-mercaptocholestan-3β-ol 3-acetate (VI) was isolated as leaflets, m.p. 167~169°, as recrystallized from $CHCl_3$-MeOH. $[\alpha]_D^{23}$ +0.5°±2° (c=1.243, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{50}O_2S$: C, 75.27; H, 10.89; S, 6.93. Found : C, 75.57; H, 10.92; S, 6.77. UV : λ_{max}^{EtOH} 208 mμ (ε 770). IR ν_{max}^{Nujol} cm^{-1} : 1728, 1271 (O-Ac).

The eluate of benzene was recrystallized from Me_2CO-MeOH to 140 mg. of 5α-mercaptocholesten-3β-ol (VII) as long needles, m.p. 168~170°, $[\alpha]_D^{23}$ +57.6°±2° (c=0.9283, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{48}OS$: C, 77.08; H, 11.50; S, 7.62. Found : C, 76.91; H, 11.60; S, 7.44. UV : λ_{max}^{EtOH} 208 mμ (ε 770). IR : ν_{max}^{Nujol} 3242 (OH) cm^{-1}.

This compound was acetylated with pyridine-Ac_2O on a steam bath for 2 hr. and the product, m.p. 141~142°, was identified with (V) by mixed m.p. and the infrared spectrum.

b) With K_2CO_3 : A solution of 200 mg. of (V) and 200 mg. of K_2CO_3 in 10 cc. of MeOH and 1 cc. of H_2O was heated under reflux. After refluxing for 10 min., leaflets appeared, then collapsed, and formed needles. After further refluxing for 20 min., the mixture was added to H_2O and extracted with Et_2O. By chromatography of the residue over 7 g. of Florisil, 20 mg. of (VI) and 140 mg. of (VII) were isolated.

Desulfurization of 5α-Mercaptocholestan-3β-ol 3,5-Diacetate (V)—To a solution of 230 mg. of (V) in 5 cc. of EtOH and 5 cc. of dioxane, 5 g. of Raney Ni was added and the mixture was heated under reflux for 8 hr. The metal was filtered off and the filtrate was evaporated. The residue was heated with 20 cc. of 5% KOH-MeOH for 1 hr. and extracted with Et_2O. Et_2O residue was chromatographed over 4.5 g. of Al_2O_3. The eluate with petr. ether-benzene (9:1) was recrystallized from Me_2CO-MeOH to 40 mg. of needles, m.p. 65~75°. $C(NO_2)_4$ test, positive. UV : λ_{max}^{EtOH} 207 mμ (ε 210). *Anal.* Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found : C, 86.79; H, 13.17. This compound was not studied further.

The residue from eluates of petr. ether-benzene (2:1-1:1) and benzene was crystallized from MeOH to 130 mg. of cholesterol, which was identified by mixed m.p. and infrared spectrum. *Anal.* Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found : C, 83.92; H, 12.03.

4-Cholesten-3-one (VIII) from 5α-Mercaptocholestan-3β-ol (VII)—a) Oppenauer oxidation : To a solution of 100 mg. of (VII) in 10 cc. of toluene, 200 mg. of (iso-PrO)$_3$Al and 1 cc. of cyclohexanone were added and the mixture was heated under reflux, when H_2S evolved. After refluxing for 8 hr., the mixture was treated as usual. The product did not crystallize and was chromatographed over 8 g. of Al_2O_3. The residue from eluate of petr. ether-benzene (19:1-1:1) was recrystallized from MeOH to 70 mg. of 4-cholesten-3-one (VIII) as needles, m.p. 80~81°, which was identified by mixed m.p. and infrared spectrum. $[\alpha]_D^{23}$ +87°±3° (c=0.644, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found : C, 84.13; H, 11.64. UV : λ_{max}^{EtOH} 242 mμ (ε 16,730). IR ν_{max}^{Nujol} cm^{-1} : 1675, 1613.

b) Pyridine-CrO_3 : To a solution of 100 mg. of (VII) in 10 cc. of pyridine, 100 mg. of CrO_3 was added. The mixture was allowed to stand overnight at room temp., H_2O added, and extracted with Et_2O-$CHCl_3$ (4:1). The extract (30 mg.) was chromatographed over 1.5 g. of Al_2O_3 and 20 mg. of crystals, m.p. 65~70°, were obtained, which recrystallized from MeOH to 4-cholesten-3-one (VIII), m.p. 80~81°. This substance was also identified by mixed m.p. and infrared spectrum.

5α-Acetylthiocholestan-3-one (IX)—A solution of 4 g. of 4-cholesten-3-one (VIII) and 400 mg. of $(Bz)_2C_2$ in 20 cc. of AcSH was allowed to stand for 5 days at room temp. and then evaporated *in vacuo*. The residue was dissolved in Et_2O, then the Et_2O solution was washed to neutrality, and evaporated. The residue was chromatographed over 120 g. of Florisil. From the eluate with petr. ether-benzene

(3:1-1:1) and benzene, 3.25 g. of 4-cholesten-3-one, m.p. 80~82°, was recovered. The residue from eluate of benzene-Et_2O was recrystallized from MeOH to 200 mg. of flat needles (IX), m.p. 180~182°. $[\alpha]_D^{23}$ +40°±3°(c=0.591, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.96. Found: C, 75.89; H, 10.78; S, 6.80. UV: λ_{max}^{EtOH} 234 mμ (ε 6,000). IR ν_{max}^{Nujol} cm^{-1}: 1720(C=O), 1689, 1118~1111 (S-Ac).

Reduction of 5α-Acetylthiocholestan-3-one (IX) with $LiAlH_4$—The compound (IX) (130 mg.) was reduced with 28 mg. of $LiAlH_4$ in 20 cc. of anhyd. Et_2O for 1 hr. and treated as above. The residue was dissolved in 1 cc. of pyridine and 1 cc. of Ac_2O, and allowed to stand overnight at room temp. A precipitate appeared in this mixture, which after addition of H_2O was extracted with Et_2O. Et_2O residue was recrystallized twice from Me_2CO to 80 mg. of leaflets (VII), m.p. 167~169°, which were identified by mixed m.p. and infrared spectrum with (VII) obtained by partial saponification of (V).

5α-Acetylthio-17β-propionyloxyandrostan-3-one (XI)—A solution of 4 g. of testosterone propionate (X) and 400 mg. of $(Bz)_2O_2$ in 5 cc. of AcSH was allowed to stand for 7 days at room temp. and evaporated *in vacuo*. The residue was dissolved in Et_2O, Et_2O solution was washed to neutrality, and evaporated to dryness. The residue was crystallized from MeOH to 750 mg. of crystals, m.p. 120~140°, which were further recrystallized twice from MeOH to 180 mg. of needles (XI), m.p. 194~196°. $[\alpha]_D^{26}$ +35.5°±3°(c=0.774, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{36}O_4S$: C, 68.53; H, 8.63; S, 7.62. Found: C, 68.63; H, 8.75; S, 7.82. UV: λ_{max}^{EtOH} 233 mμ (ε 4,900). IR ν_{max}^{Nujol} cm^{-1}: 1729, 1186(O·COEt), 1688, 1114(S-Ac).

The mother liquor was combined and chromatographed over 70 g. of Florisil. From the eluate testosterone propionate (3.5 g.) was recovered.

6β-Thiocyanatocholestane-3β,5α-diol (XIII)-A solution of 450 mg. of 5α,6α-epoxycholestan-3β-ol(XII) (m.p. 141~142°, reported[9] m.p. 141.5~142°) in 30 cc. of the HSCN-Et_2O solution was allowed to stand for 2 days at room temp. and treated as usual. The product was recrystallized from Et_2O-petr. ether to 400 mg. of needles, m.p. 182~184°, which were further recrystallized from a small amount of AcOEt to needles (XIII), m.p. 184~185°. $[\alpha]_D^{24}$ −60°±3°(c=0.652, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{47}O_2NS$: C, 72.83; H, 10.26; N, 3.03; S, 6.94. Found: C, 73.14; H, 10.28; N, 3.26; S, 6.69. IR ν_{max}^{Nujol} cm^{-1}: 3497, 3356(OH), 2165(SCN).

5α-Hydroxy-6β-thiocyanatocholestan-3-one (XIV)—To a solution of 100 mg. of (XIII) in 4 cc. of AcOH, 0.20 cc. of 12% CrO_3-AcOH was added, the mixture was allowed to stand overnight at room temp., and H_2O added. The precipitate was collected by filtration and recrystallized from MeOH to 80 mg. of needles (XIV), m.p. 181~182°. $[\alpha]_D^{24}$ −72°±3°(c=0.697, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{45}O_2NS$: C, 73.15; H, 9.87; N, 3.05; S, 6.97. Found: C, 73.42; H, 10.21; N, 3.34; S, 6.83. IR ν_{max}^{Nujol} cm^{-1}: 3448(OH), 2160(SCN), 1718(C=O).

6β-Thiocyanatocholestane-3β,5α-diol 3-Acetate (XV)—a) From the epoxide (XVI): A solution of 270 mg. of (XVI) in 30 cc. of the HSCN-Et_2O solution was allowed to stand for 2 days at room temp. and treated as usual. The product was recrystallized from MeOH to 200 mg. of rods (XV), m.p. 131~132° $[\alpha]_D^{24}$ −75°±3°(c=0.703, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{49}O_3NS$: C, 71.52; H, 9.80; N, 2.78; S, 6.36. Found: C, 71.67; H, 9.70; N, 2.92; S, 6.24. IR ν_{max}^{Nujol} cm^{-1}: 3448(OH), 2165(SCN), 1704, 1279, 1259 (O-Ac).

b) From (XIV): Acetylation of 100 mg. of (XIV) with 0.5 cc. of pyridine and 0.5 cc. of Ac_2O at room temp. overnight gave 80 mg. of rods (XV), m.p. 132~133°, which crystallized from MeOH, was identified to be the same as the above compound by mixed m.p. and the infrared spectrum.

Reduction of 6β-Thiocyanatocholestane-3β,5α-diol (XIII)—A solution of 2.30 g. of (XIII) in 50 cc. of anhyd. Et_2O and 50 cc. of tetrahydrofuran was added dropwise with stirring into a suspension of 480 mg. of $LiAlH_4$ in 30 cc. of dehyd. Et_2O during 20 min. After refluxing for 1 hr., ice and H_2O were added to the mixture. Et_2O residue was acetylated with 10 cc. of pyridine and 10 cc. of Ac_2O at room temp. overnight and the product (2.30 g.) was chromatographed over 90 g. of Al_2O_3.

From the eluate with petr. ether-benzene (3:1-1:1), 1.3 g. of crystals, m.p. 182~184°, were obtained and were recrystallized from MeOH to give cholestane-3β,5α-diol 3-acetate (XVIIa), m.p. 183~185°, $[\alpha]_D^{24}$ +9.1°±3°(c=0.656, $CHCl_3$). (reported[10] m.p. 185.5°, $[\alpha]_D$ +12.5°). *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.32; H, 11.34. IR $\nu_{max}^{CS_2}$ cm^{-1}: 3650, 3484(OH), 1733, 1244(O-Ac).

This compound was saponified with KOH-MeOH and gave cholestane-3β,5α-diol (XVIIb), m.p. 223~225°. $[\alpha]_D^{23}$ 17°±2°(c=1.00, $CHCl_3$). (reported[10] m.p. 224~225°, $[\alpha]_D$ +20.6°).

The residue from eluate of benzene and benzene-Et_2O was crystallized from MeOH to 850 mg. of needles, m.p. 128~130°, which was recrystallized three times from aq. Me_2CO to leaflets (XVIIIa), m.p. 134~136°, identified by mixed m.p. and infrared spectrum with the compound obtained by the following reaction.

9) A. Windaus: Ber., **48**, 1064(1915).
10) Pl. A. Plattner, Th. Petrzilka, W. Lang: Helv. Chim. Acta, **27**, 513(1944).

Ring-opening Reaction of 5α,6α-Epoxycholestan-3β-ol Acetate (XVI) with AcSH—A solution of 1.56 g. of (XVI) in 6 cc. of AcSH was heated under reflux for 15 hr. and extracted with Et_2O. Et_2O solution was washed to neutrality, dried over Na_2SO_4, and evaporated. The residue was crystallized from MeOH to 1.44 g. of crystals, which were recrystallized from aq. Me_2CO to 1.37 g. of leaflets (XVIIIa), m.p. 135~137°. $[\alpha]_D^{23}$ −67°±2°(c=1.008, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{52}O_4S$: C, 71.49; H, 10.06; S, 6.16. Found : C, 71.59; H, 10.09; S, 6.09. UV : λ_{max}^{EtOH} 235 mμ (ε 5,850). IR ν_{max}^{Nujol} cm^{-1}: 3451, 3341(OH), 1733, 1712, 1285, 1248(O-Ac), 1693, 1113(S-Ac).

6β-Mercaptocholestane-3β,5α-diol (XVIIIb)—a) With K_2CO_3 : A solution of 300 mg. of (XVIIIa) and 400 mg. of K_2CO_3 in 15 cc. of MeOH and 1 cc. of H_2O was heated on a steam bath for 1 hr. and H_2O added. The precipitate was collected by filtration, dried, and chromatographed over 10 g. of Florisil. The eluate with benzene gave a very small amount of crystals, which were not studied further. The residue from eluate of benzene-Et_2O was recrystallized twice from MeOH to 220 mg. of needles (XVIIIb), m.p. 188~190°. $[\alpha]_D^{23}$ −25°±2°(c=0.934, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{48}O_2S$: C, 74.25; H, 11.08; S, 7.34. Found : C, 73.97; H, 10.96; S, 7.07.

Acetylation of this compound with pyridine-Ac_2O gave the compound (XVIIIa), m.p. 134~136°, which was identified by mixed m.p. and infrared spectrum.

b) KOH : A solution of 300 mg. of (XVIIIa) in 15 cc. of 3% KOH-MeOH was heated under reflux for 1 hr., H_2O added, acidified with dil. HCl, and extracted with Et_2O. Et_2O residue, which crystallized from MeOH to a compound of m.p. 163~170°, was chromatographed over 10 g. of Florisil, and 15 mg. of cholesterol, m.p. 146~148°, and 200 mg. of (XVIIIb) were isolated.

3β-Acetoxy-5ξ-chloro-6β-acetylthiocholestane (XIX)—To a solution of 120 mg. of (XVIIIa) in 1 cc. of pyridine, 130 mg. of $SOCl_2$ was added with cooling. The mixture was allowed to stand for 1 hr. with cooling, poured into H_2O, and extracted with Et_2O. Et_2O solution was washed with dil. HCl, H_2O, Na_2CO_3 solution, and H_2O, and evaporated to dryness. The residue crystallized from Me_2CO to 60 mg. of crystals, m.p. 155~160°, which were recrystallized from Me_2CO to 30 mg. of prisms, m.p. 161~162°. *Anal.* Calcd. for $C_{31}H_{51}O_3ClS$: C, 69.05; H, 9.53; Cl, 6.57; S, 5.95. Found : C, 68.86; H, 9.51; Cl, 6.48; S, 5.86. IR ν_{max}^{Nujol} cm^{-1} : 1735, 1237(O-Ac), 1700, 1122(S-Ac), 762(C-Cl).

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Summary

Ring-opening of steroidal 5β,6β-epoxide by thiocyanic acid gave 5α-thiocyanato-6β-hydroxy compound, which was further converted to the 5α,6α-episulfide via the 5α-thiocyanato-6β-mesyloxy compound. Reduction of this episulfide with lithium aluminium hydride mainly gave cholesterol and a small amount of 5α-mercapto-3β-ol. Acetylation and saponification reaction of the latter proceeded in a different manner from those of 3β,5α-diol. Treatment of the 5α,6α-epoxide with thiocyanic acid or thiolacetic acid gave the 5α-hydroxy-6β-thiocyanato or 5α-hydroxy-6β-acetylthio compound, respectively.

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