UDC 547.92/.93

112. **Taichiro Komeno**: Bile Acids and Steroids. XV.[*2] Thiosteroids. (4). Ring-opening Reaction of 11β,12β-Episulfide with Acetic Anhydride and *p*-Toluenesulfonic Acid.

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In Part XIV (3) of this series,[1] it was shown that 11β,12β-episulfides could not be reductively cleaved to 11β-mercapto derivatives by various reagents such as lithium aluminium hydride, sodium-amalgam, etc., but was desulfurized to a 11-olefin under drastic conditions. The present paper describes further studies on the 11β,12β-episulfide.

When 11β,12β-epithiocholane-3α,24-diol (I) was treated with acetic anhydride and *p*-toluenesulfonic acid[*3] at room temperature, a compound (II), m.p. 113~115°, was obtained in a good yield. This compound exhibited absorptions at 1694 and 1131 cm^{-1} besides those due to O-acetate groups in its infrared spectrum and an absorption maximum at 235 mμ (ε 5,400) in the ultraviolet spectrum. Since these spectral data agree well with those observed for simple thiol esters[2] and from the analytical data, the compound (II) was assumed to be a mercapto-diol triacetate. Saponification of the compound (II) with alkali yielded a free mercapto-diol (III), m.p. 146~148°, accompanied by a small amount of a substance (IV), m.p. 236~238° (decomp.), while the former compound (III) was also obtained by reduction of the triacetate (II) with lithium aluminium hydride. The free mercapto-diol (III) gave the parent triacetate (II) by acetylation with pyridine and acetic anhydride. The compound (IV), m.p. 236~238° (decomp.), was obtained in a nearly quantitative yield by oxidation of the free mercapto-diol with iodine and it was also obtained in a low yield by treatment of the epithio-diol (I) with *p*-toluenesulfonic acid in dioxane. It is known that simple dialkyl disulfides exhibit an absorption maximum at 250 mμ (ε 400~560) in the ultraviolet spectrum[3] and a shoulder was observed at 270 mμ (ε 560) in the ultraviolet spectrum of this compound (IV). From these chemical conversions, molecular weight determination, and ultraviolet absorption, the compound (IV) was assumed to be a dithio-bis-diol.

On the other hand, when the triacetate (II) was desulfurized with Raney nickel or reduced with lithium-ethylamine, 9(11)-lithocholenyl alcohol 3,24-diacetate (Va) or its free diol (Vb) was obtained. Reduction of the dithio-bis-diol (IV) with lithium-ethylamine also gave the same 9(11)-ene-diol. Birch[4] stated that esters of allyl alcohols in general are reduced readily to olefins with lithium-ethylamine and benzyl alkyl sulfide is reduced to alkanethiol and toluene with these reagents. Henbest, *et al.*[5] also reported that 3β-acetoxy-4-cholestene and 6β-acetoxy-4-cholestene both gave a mixture of 5-cholestene and 4-cholestene by the action of lithium-ethylamine. From these data it appears probable that the mercapto-diol (III) is a 12β-mercapto-9(11)-cholene-3α,24-diol and dithio-

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[*2] Part XIV. K. Takeda, T. Komeno, J. Kawanami: This Bulletin, 8, 621(1960).

[*3] 11β-Alcohols and tertiary alcohols are acetylated by this procedure (E. P. Oliveto, E. B. Hershberg: J. Am. Chem. Soc., 75, 5486(1953)). This method was attempted here, because the compound (I) had been mistaken as 11β-mercapto derivative.

1) K. Takeda, T. Komeno, J. Kawanami: This Bulletin, 8, 621(1960).

2) 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).

3) H. P. Koch: J. Chem. Soc., **1949**, 394; J. A. Barltrop, P. M. Hayes, M. Calvin: J. Am. Chem. Soc., **76**, 4348(1954).

4) A. J. Birch, H. Smith: Quart. Revs., **12**, 17(1958).

5) A. S. Hallsworth, H. B. Henbest, T. I. Wrigley: J. Chem. Soc., **1957**, 1969.

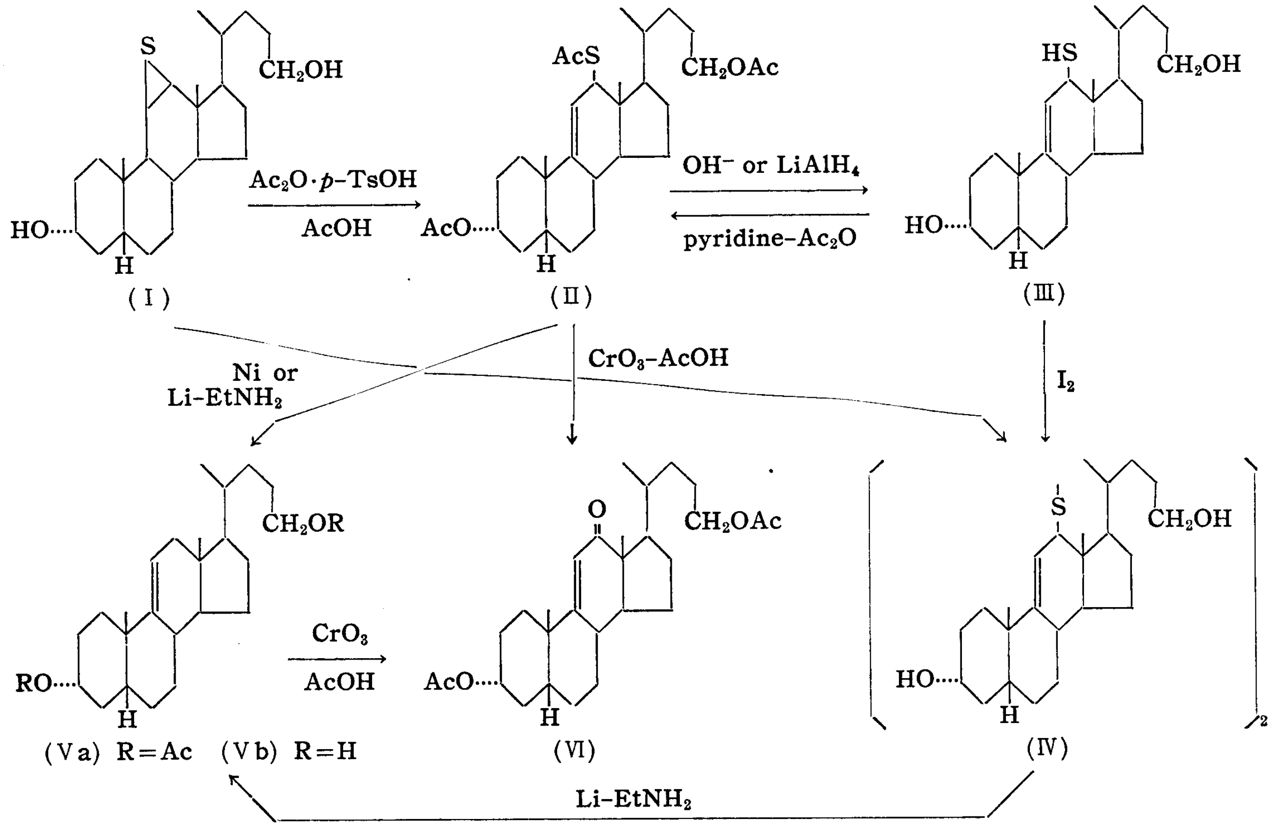

Chart 1.

bis-diol, 12β,12′β-dithio-bis(9(11)-cholene-3α,24-diol). These assumptions were also confirmed by the following reaction. Oxidation of the triacetate (II) with chromium trioxide gave an α,β-unsaturated ketone (VI), m.p. 128~130°, which exhibited an absorption maximum at 240 mμ (ε 10,700) in its ultraviolet spectrum and was identified as 3α,24-diacetoxy-9(11)-cholen-12-one, obtained by oxidation of 9(11)-lithocholenyl alcohol 3,24-diacetate (Va) with chromium trioxide.[*4]

Configuration of the 12-mercapto group was assumed to be β from consideration of the reaction mechanism shown in Chart 2.[*5,6]

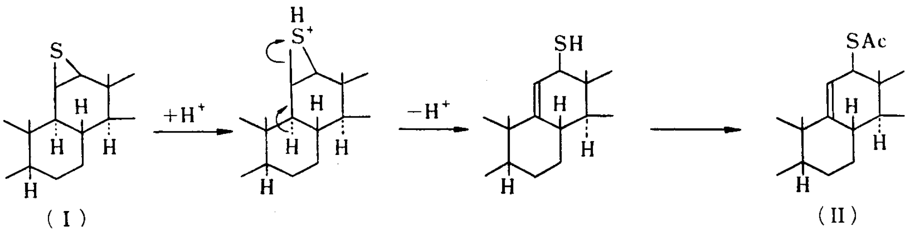

Chart 2.

[*4] E. Seebeck and T. Reichstein (Helv. Chim. Acta, **26**, 536(1943)) reported that methyl 3α-acetoxy-9(11)-cholenate was oxidized with chromium trioxide to methyl 3α-acetoxy-12-oxo-9(11)-cholenate.

[*5] Formation of (IV) from (I) may be ascribed to the impurity of dioxane used as a solvent, because Djerassi found that simple thiols were oxidized to disulfides by treatment with impure dioxane (J. Am. Chem. Soc., **79**, 2553(1957)).

[*6] The assumption that in this case the transannular hydrogen transfer, found in the acid-catalyzed rearrangement of a 9β,11β-epoxide to a homoallyl alcohol (8(14)-en-11β-ol) (N. L. Wendler, R. P. Graber, C. S. Snoddy, F. W. Bollinger: J. Am. Chem. Soc., **79**, 4476(1957)) will occur, may be neglected, because it does not appear that the product (8(9)-ene-12β-thiol), which presumably is formed, rearranges to 9(11)-ene-12β-thiol in the condition with lithium-ethylamine; for instance it was reported[5] that a 9(11)-ene-5,8-peroxide was reduced to 8(9)-en-5α-ol in the same conditions.

This assignment was also supported from the molecular rotation difference (Table I).

Table I. Molecular Rotation Difference

	M_D		ΔSH		ΔSAc
12β-Mercapto-9(11)-cholene-3α,24-diol (III)	+ 23	III−Vb	−157		
12β-Mercapto-9(11)-cholene-3α,24-diol 3,12,24-triacetate (II)	−0.3				
9(11)-Lithocholenyl alcohol (Vb)[a]	+180			II−Va	−258
9(11)-Lithocholenyl alcohol 3,24-diacetate (Va)[a]	+258				
			ΔOH		ΔOAc
9(11)-en-12β-ol[b]			− 65		−256
			ΔOH		ΔOAc
9(11)-en-12α-ol[b]			+232		+705

a) L. F. Fieser, S. Rajagopalan: J. Am. Chem. Soc., **73**, 118(1951).
b) W. Klyne: Helv. Chim. Acta, **35**, 1224(1952).

Experimental[*7]

12β-Mercapto-9(11)-cholene-3α,24-diol 3,12,24-Triacetate (II)—To a solution of 500 mg. of the 11β,12β-episulfide (I) in 5 cc. of AcOH, 100 mg. of *p*-TsOH and 5 cc. of Ac_2O were added. The reaction mixture was allowed to stand overnight at room temp., H_2O added, and extracted with Et_2O. The Et_2O solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from MeOH to 530 mg. of flat needles, m.p. 113~115°. $[\alpha]^{26}_D$ −0.1°±3° (c=0.580, dioxane). *Anal.* Calcd. for $C_{30}H_{46}O_5S$: C, 69.46; H, 8.94; S, 6.18. Found: C, 69.10; H, 8.96; S, 6,32. UV: λ^{EtOH}_{max} 235 mμ (ε 5,430). IR $\nu^{CCl_4}_{max}$ cm^{-1}: 1739 (O-Ac), 1694 (S-Ac).

12β-Mercapto-9(11)-cholene-3α,24-diol (III)—a) The triacetate (II) (330 mg.) dissolved in 10 cc. of 3% KOH-MeOH was heated under reflux for 3 hr., H_2O added, and acidified with dil. HCl. The precipitate was collected by filtration, dried, and crystallized from hydr. Me_2CO to 240 mg. of crystals (III), m.p. 146~148°. $[\alpha]^{27}_D$ +5.9°±3° (c=0.746, dioxane). *Anal.* Calcd. for $C_{24}H_{40}O_2S$: C, 73.42; H, 10.27; S, 8.17. Found: C, 73.23; H, 10.31; S, 8.04.

Saponification was also carried out with K_2CO_3-MeOH and gave the same results.

In another run, an impure saponification product (400 mg.) was purified by chromatography over 12 g. of Florisil and from the eluate with benzene and benzene-Et_2O (98:2-9:1), 320 mg. of crystals (III), m.p. 146~148°, was obtained. The eluate with benzene-Et_2O (8:2-1:1) gave 30 mg. of crystals (IV), m.p. 235~238° (decomp.).

The compound (III), m.p. 146~148°, was acetylated with pyridine-Ac_2O overnight at room temp. or heating for 2 hr. on a steam bath, to give the triacetate (II), m.p. 113~115°, which was identified by mixed m.p. and infrared spectrum.

b) To a suspension of 300 mg. of $LiAlH_4$ in 10 cc. of dehyd. Et_2O, a solution of 760 mg. of (II) in 20 cc. of dehyd. Et_2O was added dropwise with stirring over a period of 20 min. After refluxing for 1 hr., ice was added to the reaction mixture to destroy the excess reagent. The Et_2O solution was washed with HCl, H_2O, Na_2CO_3 solution, and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from Me_2CO to 480 mg. of crystals (III), m.p. 146~148°, which was identified with the compound obtained by method a) by mixed m.p. and infrared spectrum.

12β,12′β-Dithio-bis(9(11)-cholene-3α,24-diol) (IV)—a) From (III): To a solution of 100 mg. of (III) in 5 cc. of EtOH, 35 mg. of I_2 was added in small quantities. From the mixture a precipitate appeared readily and was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with $Na_2S_2O_3$ solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from Me_2CO to 90 mg. of crystals, m.p. 236~238° (decomp.). *Anal.* Calcd. for $2(C_{24}H_{39}O_2S)$: C, 73.60; H, 10.04; S, 8.19; mol. wt., 783.3. Found: C, 73.58; H, 9.98; S, 7.92; mol. wt., (Rast; Δt=5.2°), 755.2. UV: λ^{EtOH}_{max} 270 mμ (ε 560) (shoulder).

b) From (I): A solution of 400 mg. of (I) and 80 mg. of *p*-TsOH in 12 cc. of dioxane was allowed to stand for 2 days at room temp., H_2O added, 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 to 50 mg. of crystals (IV), m.p. 235~237°, which were identified with the compound obtained by method a) by mixed m.p. and infrared spectrum.

[*7] All m.p.s were determined in capillary tubes and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Single-beam Infrared Spectrophotometer, Model 12C, and ultraviolet spectra were taken with a Beckman Spectrophotometer, Model DU.

The mother liquor was concentrated and gave 190 mg. of the starting material, m.p. 157~162°. The mother liquor was evaporated to dryness and acetylated with pyridine-Ac_2O as usual. The product gave 90 mg. of the diacetate of the starting material, m.p. 108~110°. These compounds were identified by mixed m.p. and infrared spectra.

9(11)-Lithocholenyl Alcohol (Vb)—a) From (II): To a solution of 250 mg. of (II) in 6 cc. of dioxane, 5 g. of freshly prepared Raney Ni was added. The mixture was heated under reflux for 8 hr., Ni was filtered off, and evaporated. The residue was crystallized from hydr. MeOH to 100 mg. of leaflets (Va), m.p. 90~92°($C(NO_2)_4$-test, positive), which was identified as 9(11)-lithocholenyl alcohol 3,24-diacetate by mixed m.p. and infrared spectrum. *Anal.* Calcd. for $C_{28}H_{44}O_4$: C, 75.63; H, 9.97. Found: C, 75.83; H, 10.23.

The mother liquor was heated under reflux for 2 hr. with 300 mg. of K_2CO_3 in hydr. MeOH. The mixture was added to H_2O, the precipitate was collected by filtration, and recrystallized from AcOEt to 70 mg. of 9(11)-lithocholenyl alcohol, m.p. 179~180°, which was identified by mixed m.p. and infrared spectrum. *Anal.* Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18; O, 8.88. Found: C, 80.07; H, 11.23; O, 9.18.

To a solution of 240 mg. of (II) in 40 cc. of $EtNH_2$, 170 mg. of Li was added in small quantities with stirring under cooling. After agitation for 1.5 hr., the mixture was completely decolorized, evaporated, ice and dil. HCl added, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with Na_2CO_3 solution and H_2O, and evaporated to dryness. The residue was recrystallized from AcOEt to 130 mg. of (Vb), m.p. 177~179°, which was identified by mixed m.p. and the infrared spectrum.

b) From (IV): The disulfide (IV)(130 mg.) was treated as above with 100 mg. of Li in 30 cc. of $EtNH_2$. In this case, the reaction mixture was decolorized after agitation for 40 min. The same treatment as above gave 100 mg. of (Vb), m.p. 178~179°, which was identified by mixed m.p. and infrared spectrum.

3α,24-Diacetoxy-9(11)-cholen-12-one (VI)—a) From (Va): To a solution of 380 mg. of (Va) in 4 cc. of AcOH, 144 mg. of CrO_3 was added. The mixture was allowed to stand overnight at room temp., H_2O added, and extracted with Et_2O. The Et_2O solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue, crystallized from petr. ether to crystals of m.p. 120~125°, was chromatographed over 11 g. of Al_2O_3. From the eluate with petr. ether-benzene (9:1–2:1) 200 mg. of the starting material, m.p. 80~85°, was recovered, and from the eluate with benzene, 110 mg. of leaflets (VI) were obtained, and were recrystallized from hydr. MeOH, m.p. 128~130°. $[\alpha]_D^{30}$ +95.2°±3°(c=0.713, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{42}O_5$: C, 73.33; H, 9.23. Found: C, 73.20; H, 9.29. UV: λ_{max}^{EtOH} 240 mμ (ε 10.720). IR ν_{max}^{Nujol} cm^{-1}: 1749, 1735, 1670, 1606, 1245.

b) From (II): The triacetate (II)(200 mg.) was oxidized with 130 mg. of CrO_3 in 4 cc. of AcOH as described above. By chromatography over Al_2O_3, 80 mg. of the starting material, m.p. 110~115°, and 100 mg. of (VI), m.p. 128~130°, were separated. The latter was identified with the compound prepared by method (a) by mixed m.p. and infrared spectrum.

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Summary

Treatment of 11β,12β-epithiocholane-3α,24-diol (I) with acetic anhydride and *p*-toluenesulfonic acid gave 12β-acetylthio-9(11)-olefin (II), structure of which was assumed by its chemical conversion into the 9(11)-ene or 9(11)-en-12-one compound and also by comparison of molecular rotation differences between the 12-mercapto-9(11)-ene and the corresponding alcohols.

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