STUDIES IN ORGANIC SULFUR COMPOUNDS XV.*
A NOVEL BASE-CATALYZED REARRANGEMENT OF A STEROID β-KETO-XANTHATE

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Alkaline treatment of cholestan-3-one-2α-ethylxanthate gave among four products, the unexpected 2-thioncarbethoxy-Δ^2-cholesten-3-ol. This reaction of generating a carbon-carbon bond, heretofore unreported in the steroid field, affords a novel method of preparing thiono-esters.

In the course of our recent studies on the synthesis[1,2] and the rotatory dispersion and circular dichroism properties[3] of a large number of steroidal xanthates, episulfides and trithiocarbonates, we had occasion to treat cholestan-3-one-2α-ethylxanthate (I) with base in order to determine the configuration at C-2, which at that time[4] had not been proven chemically. Thus, if the xanthate had been the axial 2β-epimer, it presumably would have been epimerized to the more stable α-configuration; whereas, if the xanthate had been the equatorial 2α-isomer, it would have been expected to be recovered unchanged. Upon treatment with ethanolic potassium hydroxide an immediate and facile reaction ensued, and subsequent investigation of the reaction products indicated that the keto-xanthate (I) had undergone a total rearrangement or decomposition. Aside from sulfur, there were isolated three products, whose constitution was shown to be 2-thioncarbethoxy-Δ^2-cholesten-3-ol (II), bis-cholestan-3-one-2,2'-disulfide (III) and cholestan-3-one-2α-thiol (IV). The last substance was present in very small amounts and likely reacted in the basic solution to give the disulfide III by air oxidation.

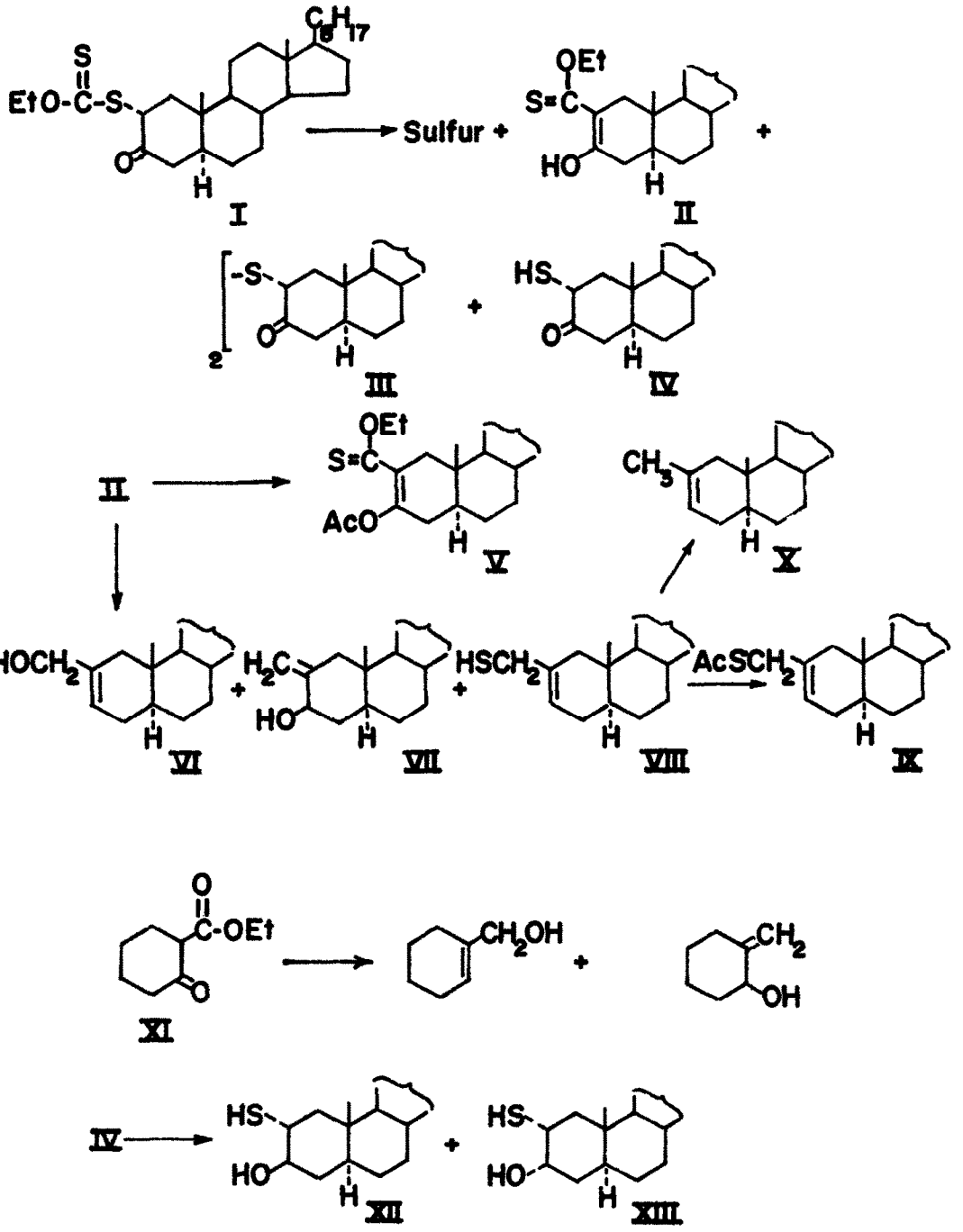
The structure of II was determined by both physical and

chemical means. The mass spectrum gave a molecular ion peak at m/e 474; this in conjunction with the elemental analysis, ($C_{30}H_{50}O_2S$) suggested simply a loss of sulfur from the parent compound I ($C_{30}H_{50}O_2S_2$). The ultraviolet spectrum with an intense absorption at 328 mμ, pointed towards the existence of a conjugated chromophore, which was shown subsequently to involve the thione grouping.

The structure of the enol II, which could be acetylated to an O-acetate V was proved chemically by lithium aluminum hydride reduction to give three products: the known[5] 2-hydroxymethyl-Δ^2-cholestene (VI), the independently synthesized 2-methylenecholestan-3β-ol (VII) and 2-mercaptomethyl-Δ^2-cholestene (VIII). The thiol VIII could be acetylated to give an S-acetate (IX) and also gave the known[5] 2-methyl-Δ^2-cholestene (X) by Raney nickel desulfurization; whereas, the alcohol VII was synthesized by lithium aluminum hydride reduction of 2-hydroxymethylenecholestan-3-one.[5] Reassembling the reduction fragments VI, VII and VIII, and barring any unprecedented rearrangements in the reduction, requires attachment to C-2 of a carbon atom bearing sulfur as well as oxygen. In addition, an oxygen atom is required at C-3. The structure of the enol II satisfies these requirements as well as the physical data, and its reduction to compounds VI-VIII is in agreement with the results obtained by Dreiding and Hartman[6] in the reduction of 2-carbethoxycyclohexanone (XI).

The structures of the disulfide III and the keto-thiol IV were proven in the following manner. Acid treatment of cholestan-3-one-2α-ethylxanthate (I) gave the keto-thiol IV directly in high yield. This keto-thiol IV could be reduced by lithium aluminum hydride to the known[4,7] cholestan-3β-ol-2α-thiol (XII) and the unreported cholestan-3α-ol-2α-thiol (XIII).

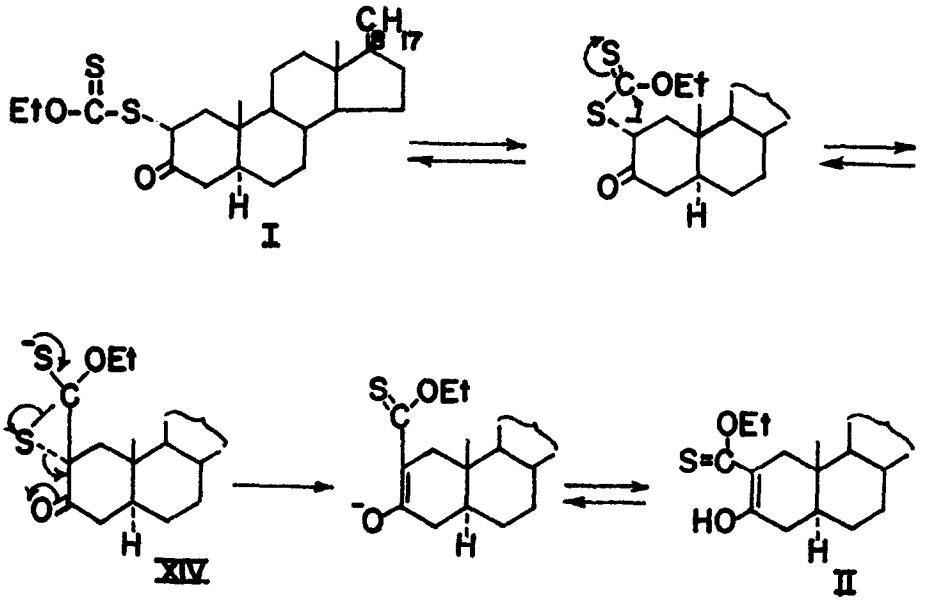
The latter hydroxy-thiol XIII was synthesized independently from 3α-acetoxycholestan-2α-ethylxanthate[1] by lithium aluminum hydride reduction. The keto-thiol IV was sensitive to air when in solution, whereupon it was transformed into



the disulfide III.

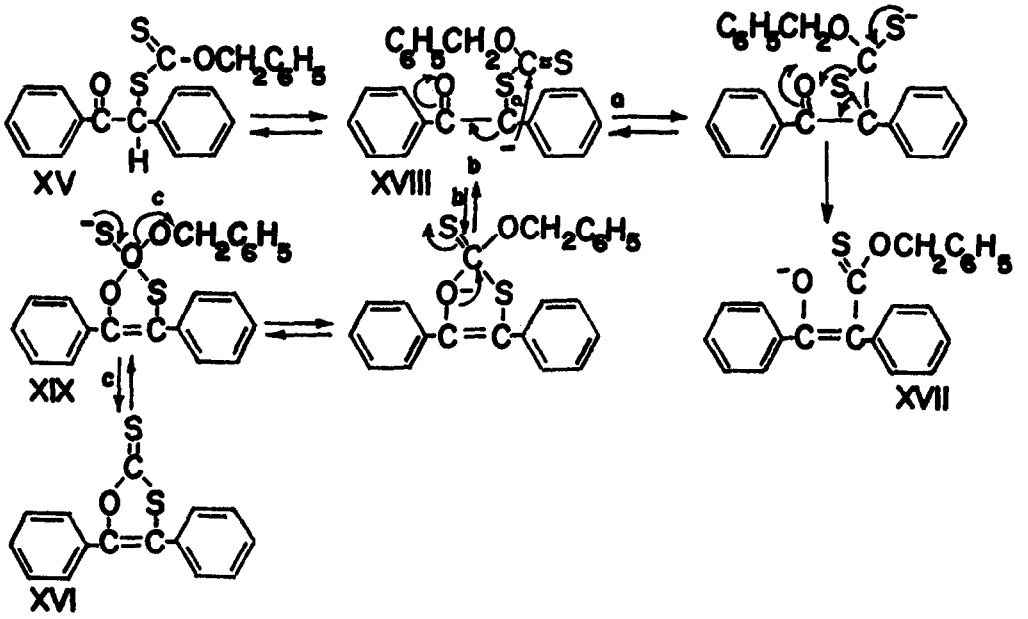
The mechanism of formation of the enol II is probably

analogous to the base-catalyzed rearrangement of 3-methyl-2-phenacylthiobenzothiazolium bromide reported by Knott.[8] Thus, abstraction of the acidic proton at C-2 of I gives an anion which may attack the thione carbon atom to produce an episulfide-like intermediate (XIV). Collapse of XIV with extrusion of sulfur and O-protonation would lead to the isolated enol II.



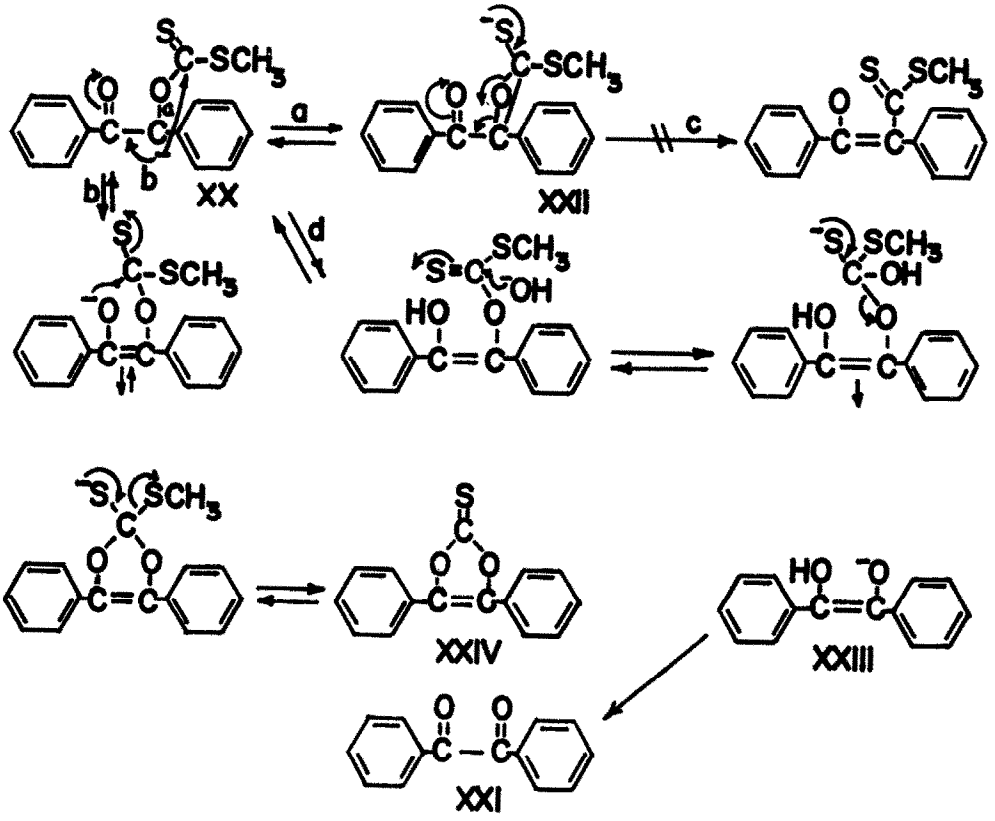
Further studies were initiated to determine the parameters affecting this novel rearrangement as well as its generality. To this end desyl benzylxanthate[4] (XV) was synthesized and treated with base in aqueous dioxane. Such treatment led to the unexpected dithiocarbonate XVI as well as to what is probably a mixture of keto-thiol and its corresponding disulfide with no trace of the expected rearrangement product XVII. The mechanism of rearrangement for the formation of XVII likely requires the existence of intermediate XVIII, which can react by either path (a) or

path (b). Path (a) leads ultimately to XVII, whereas path (b) terminates by XVI. In an equilibrium sequence in which the relative rates are similar, the lowest energy pathway will play the major role in the determination of the eventual products. In this particular case, there can be little doubt that path (b), which affords greater electron delocalization by means of the stilbene intermediate XIX, is the path of lower energy, and the ultimate product through this intermediate is XVI.



The question as to whether similar types of rearrangements will occur when the xanthate oxygen rather than sulfur atom is attached α to the carbonyl group was partially resolved by base-treatment of benzoin S-methylxanthate (XX), although, perhaps more pertinent information could be gained from similar treatment of non-aromatic systems. Thus, benzoin S-methylxanthate (XX)[9] when treated with methanolic potassium hydroxide gave benzil (XXI) in high yield. In the reaction sequence indicated, path (a) is blocked from reacting through route (c) inas-

much as intermediate XXII is not likely to expel oxygen. Alternatively, and perhaps simultaneously or exclusively, path (b) can lead to product XXIV; whereas, path (d) gives the benzoin anion (XXIII) in an irreversible step. In any event, it is likely that the S-methylxanthate XX decomposes ultimately to XXIII, which is easily air-oxidized[10] in the basic medium to benzil (XXI).



It may be concluded that a rearrangement of the type giving enol (II) will occur with suitable β-keto-xanthates in the absence of special considerations, such as those encountered with desyl benzylxanthate (XV). It is also necessary that the carbon α to the ketone be attached to the sulfur of the xanthate and not to the oxygen atom, in order that sulfur may be eliminated or that a less strained episulfide intermediate (vs. an epoxide) may be formed.

Whether a thione group is necessary in the xanthate or whether it may be substituted by a carbonyl function has not been determined.

EXPERIMENTAL

All melting points were obtained with a Thomas Hoover capillary melting point apparatus and are uncorrected unless otherwise indicated. The microanalyses are due to Messrs. E. Meier and J. Consul of the Stanford University Microanalytical Laboratory. The mass spectra were obtained by Drs. H. Budzikiewicz, J. M. Wilson and M. Ohashi. All thin-layer chromatograms (TLC) were performed with silica gel G (E. Merck, Darmstadt) and sprayed with a 10% solution of ammonium molybdate in 10% sulfuric acid.

Base Treatment of Cholestan-3-one-2α-ethylxanthate (I). - To cholestan-3-one-2α-ethylxanthate (1.613 g., 3.2 mmoles) dissolved in 10 ml. of ether and 25 ml. of ethanol was added 10 ml. of 2 N ethanolic potassium hydroxide. After standing at room temperature for 0.75 hr., the mixture was poured into ice-diluted hydrochloric acid (containing 15 ml. of 5% hydrochloric acid). This mixture was extracted with chloroform and the chloroform layer was washed well with water, dried over anhydrous magnesium sulfate and evaporated. The resulting orange semi-solid weighed 1.670 g. This was chromatographed on 80 g. of silica gel, using gradient elution. To a 500 ml. reservoir of n-hexane was added 250 ml. each of 1:3, 1:1 and 3:1 chloroform-hexane, taking 25 ml. fractions. Fractions 2, 3 and 4 gave 44 mg. (1.38 mmoles) of sulfur, m.p. 120-121°. Fractions 5-15 gave 800 mg. (1.68 mmoles) of 2-thioncarbethoxy-Δ^2-cholesten-3-ol, m.p. 96-97° (oil solidified, but could not be crystallized); $[\alpha]_D^{26}$ +79° (c. 1.22, chloroform); ν_{max} 1580, 1200, 1028, 771 cm.$^{-1}$ (KBr); log ε_{328}^{max} 4.13, log ε_{271}^{min} 1.95, log ε_{249}^{max} 3.77, log ε_{224}^{min} 2.20 (n-hexane).

Anal. Calcd. for $C_{30}H_{50}O_2S$ (474.76): C, 75.90; H, 10.62;

S, 6.78; O, 6.70. Found: C, 75.61; 75.33; H, 10.49; 10.56; S, 6.90; O, 6.88.

Pure chloroform eluted 622 mg. of a mixture of cholestan-3-one-2α-thiol and its corresponding disulfide with the disulfide predominating. Separation of this latter mixture by repeating the column chromatography gave 39 mg. of cholestan-3-one-2α-thiol (IV), m.p. 160-162°, (0.093 mmole) and 477 mg. (0.57 mmole) of the disulfide III, m.p. 228-229°. The total steroid recovered was 2.91 mmoles (counting two times the disulfide).

2-Thioncarbethoxy-Δ^2-cholesten-3-ol acetate (V). - To 2-thioncarbethoxy-Δ^2-cholesten-3-ol (200 mg., 0.423 mmole) in 5 ml. of pyridine was added 0.5 ml. of acetic anhydride. The solution was allowed to stand at room temperature for 48 hr., during which time it became yellow and deposited yellow needles. After cooling to -15°, the needles were filtered and dried to yield 190 mg. (87%) of the acetate which was pure by thin-layer chromatography (85% benzene - 15% hexane). The acetate melted at 178-179°; $[\alpha]_D^{25}$ +89.7° (c.107, chloroform); ν_{max} 1755, 1635, 1282, 1265, 1230, 1210, 1145, 1105, 1010, 949, 592 cm.$^{-1}$ (KBr); log ε_{396}^{max} 2.13, log ε_{352}^{min} 1.54, log ε_{282}^{max} 4.06, log ε_{230}^{min} 3.53 (dioxane).

Anal. Calcd. for $C_{32}H_{52}O_2S$ (516.81): C, 74.36; H, 10.14; S, 6.21. Found: C, 74.32; H, 10.12; S, 6.26.

Lithium Aluminum Hydride Reduction of 2-Thioncarbethoxy-Δ^2-cholesten-3-ol (II). - To a solution of 2-thioncarbethoxy-Δ^2-cholesten-3-ol (1.0 g., 2.1 mmoles) in 150 ml. of anhydrous ether was added excess lithium aluminum hydride and the mixture was heated at reflux for 42 hr. (a lesser time gave less complete reduction). Saturated aqueous sodium sulfate was added to destroy the excess hydride and the mixture was heated under reflux for one hr. The reaction mixture was cooled, washed with 2% hydrochloric acid, water, dried over anhydrous magnesium sulfate and evaporated to yield about 1 g. of a gum. This material was chromatographed on 80 g. of

silica gel, using gradient elution. To a 500 ml. reservoir of n-hexane was added 200 ml. each of 5%, 7.5%, 10%, 15%, 20% and 40% ether-hexane, taking 25 ml. fractions. Fractions 5-10 gave 490 mg. (56%) of 2-mercaptomethyl-Δ^2-cholestene (VIII) as an uncrystallizable oil; $[\alpha]_D^{25}$ +4° (c. 0.76, chloroform).

This thiol was further characterized by its acetate IX.

Fractions 50-59 eluted 214 mg. (26%) of a mixture of two alcohols. These alcohols were separated by repeated preparative thin-layer chromatography (100% methylene chloride). This procedure gave 42 mg. (5%) of 2-hydroxymethyl-Δ^2-cholestene (VI) and 100 mg. (12%) of 2-methylene-cholestan-3β-ol (VII).

The 2-hydroxymethyl-Δ^2-cholestene (VI) had m.p. 138-139°; mixture m.p. with authentic material,[5] 137-139°; $[\alpha]_D^{26}$ +61.2° (c. 0.83, chloroform); (Lit. m.p.[5] 140-142°; $[\alpha]_D$ +63°).

The 2-methylene-cholestan-3β-ol (VII) had m.p. 135-136°, and 133-135° upon admixture with authentic material; $[\alpha]_D^{27}$ -1° (c. 0.99, chloroform).

2-Mercaptomethyl-Δ^2-cholestene acetate (IX). - 2-Mercaptomethyl-Δ^2-cholestene (88 mg., 0.21 mmole) was dissolved in 5 ml. of pyridine and to this solution was added 0.5 ml. of acetic anhydride. The solution was allowed to stand at room temperature for 5 days, after which time it was diluted with ether and washed well with water. The ether was dried over anhydrous magnesium sulfate and evaporated to give an oil which was chromatographed on 15 g. of silica gel. Hexane eluted 17 mg. of unreacted thiol. Ether (2%)-hexane gave 71 mg. (74%) of acetate, m.p. 54-56°; $[\alpha]_D^{23}$ +43° (c. 1.32, chloroform); ν_{max} 1685, 1128, 1094, 950, 700, 620 cm.$^{-1}$ (KBr).

Anal. Calcd. for $C_{30}H_{50}OS$ (458.76): C, 78.55; H, 10.99; S, 6.97. Found: C, 78.69; H, 11.05; S, 7.05.

Raney Nickel Desulfurization of 2-Mercaptomethyl-Δ^2-cholestene (VII). - 2-Mercaptomethyl-Δ^2-cholestene (48 mg., 0.115 mmole) was stirred at reflux with 0.5 g. of W-2 Raney

nickel (two weeks old) in 25 ml. of benzene for 15 hr. This reaction mixture was cooled, filtered through Celite and the solvent evaporated to give 48 mg. of a solid, m.p. 89-94°. This solid was chromatographed on Woelm neutral alumina (Act. 1). Pentane eluted 36 mg. (86%) of 2-methyl-Δ^2-cholestene (X), m.p. 99-100°. A mixture melting point with authentic material was 97-99°. The compound had $[\alpha]_D^{27}$ +66° (c. 0.98, chloroform); (Lit.[5] m.p. 100-101°; $[\alpha]_D$ +68°).

2-Methylenecholestan-3β-ol (VII). - A solution of 2-hydroxymethylene-cholestan-3-one (1.7 g., 4.12 mmoles) in 200 ml. of anhydrous ether was added to a slurry of 2.0 g. of lithium aluminum hydride in 300 ml. of ether. Stirring was continued for 2 hr. at room temperature. The excess hydride was destroyed with ethyl acetate, then saturated aqueous sodium sulfate was added. After filtration of the solids, the ether filtrate was washed with water, dried over anhydrous magnesium sulfate and evaporated to give 1.5 g. of a white solid which was chromatographed on 90 g. of Florisil (60/100 mesh, Floridan Co., Tallahassee, Florida), using gradient elution. To a 500 ml. reservoir of n-hexane was added 500 ml. of 1:1 hexane-chloroform, the pure chloroform collecting 30 ml. fractions. Fractions 32-39 gave 900 mg. of slightly impure alcohol, which was rechromatographed on 100 g. of silica gel, using gradient elution. To a 500 ml. reservoir of n-hexane was added 250 ml. each of 1:4, 1:3, 1:1, 3:1 chloroform-hexane, collecting 30 ml. fractions. Fractions 48-58 gave 723 mg. (44%) of pure alcohol, m.p. 133-134°, $[\alpha]_D^{25}$ -3° (c. 0.91, chloroform); ν_{max} 3300, 1645, 1085, 1070, 1035, 888 $cm.^{-1}$ (KBr).

Anal. Calcd. for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 83.67; H, 11.94.

Cholestan-3-one-2α-thiol (IV). - A slow stream of dry hydrogen chloride gas was passed through a solution of cholestan-3-one-2α-ethylxanthate (3.0 g., 5.9 mmoles) in 50 ml. of anhydrous ether for 30 min. The solution was

allowed to stand in a closed vessel at room temperature for 48 hr. The ether was evaporated on the steam bath under a stream of nitrogen. The solid residue was chromatographed on 150 g. of silica gel, using gradient elution. To a 500 ml. reservoir of n-hexane was added 300 ml. of 20% methylene chloride-hexane, 250 ml. of 30% methylene chloride-hexane, 250 ml. of 50% methylene chloride-hexane, then 1:1 methylene chloride-ether, taking 30 ml. fractions. Fractions 26 through 46 gave 1.84 g. (74%) of cholestan-3-one-2α-thiol, m.p. 160-163°; $[\alpha]_D^{27}$ +50° (c. 1.06, chloroform); ν_{max} 2550, 1704, 587 $cm.^{-1}$ (KBr); log ε_{280}^{max} 3.02, log ε_{257}^{min} 2.64 (dioxane).

Anal. Calcd. for $C_{27}H_{46}OS$ (418.706): C, 77.45; H, 11.07; S, 7.66. Found: C, 77.20; H, 10.89; S, 7.75.

Bischolestan-3-one-2,2'-disulfide (III). - Cholestan-3-one-2α-thiol (68 mg., 0.0163 mmole) was dissolved in 10 ml. of ethanol and 6 ml. of chloroform. To this solution was added a few mg. of anhydrous ferric chloride and a slow stream of air was passed through the solution for 12 hr. Ether was then added, the solution washed well with water, the ether dried over anhydrous magnesium sulfate and evaporated. Crystallization of the resultant crude solid from methylene chloride-hexane gave 40 mg. (59%) of the disulfide, m.p. 227-228°; $[\alpha]_D^{27}$ -88.9° (c. 1.08, chloroform); ν_{max} 1702, 585 $cm.^{-1}$ (KBr); log $\varepsilon_{280}^{shoulder}$ 2.61 (dioxane).

Anal. Calcd. for $C_{54}H_{90}O_2S_2$ (834.39): C, 77.63; H, 10.86; S, 7.68; O, 3.83. Found: C, 77.52; H, 10.86; S, 7.63. Molecular weight (thermistor method - vapor pressure osmometer) in chloroform: 702.

Lithium Aluminum Hydride Reduction of Cholestan-3-one-2α-thiol (IV). - Cholestan-3-one-2α-thiol (220 mg., 0.525 mmole) was dissolved in 15 ml. of anhydrous ether and to this solution was added excess lithium aluminum hydride. The mixture was stirred at room temperature for 15 min., then 5% hydrochloric acid and ether were added. The ether

layer was washed well with water, dried over anhydrous magnesium sulfate and evaporated. The resultant residue was chromatographed on 30 g. of silicic acid, using gradient elution. To a 250 ml. reservoir of n-hexane was added 200 ml. each of 1:3, 1:1 and 3:1 methylene chloride-hexane, taking 20 ml. fractions. Fractions 19 through 23 gave 38 mg. of cholestan-3α-ol-2α-thiol. Crystallization from ether-methanol gave crystals, m.p. 119-120° and 118-120° upon admixture with authentic material.

Fractions 24-30 eluted 95 mg. of cholestan-3β-ol-2α-thiol. This material was crystallized from ether-methanol to give crystals melting at 125-127° and 125-127° upon admixture with authentic material; (Lit. m.p.[4] 122-124°; $[\alpha]_D^{25}$ +10.6°).

Cholestan-3α-ol-2α-thiol (XIII). - To cholestan-3α-ol acetate 2α-ethylxanthate (155 mg., 0.25 mmole) in 50 ml. of anhydrous ether was added excess lithium aluminum hydride and the mixture was heated at reflux for 6 hr. Saturated aqueous sodium sulfate was added to destroy the excess hydride; then ether and 5% hydrochloric acid were added. The ether layer was washed well with water, dried over anhydrous magnesium sulfate and evaporated to yield 95 mg. (81%) of cholestan-3α-ol-2α-thiol after one crystallization from ether-methanol, m.p. 119-120°; $[\alpha]_D^{26}$ +25.7° (c. 1.09, chloroform); ν_{max} 3400, 1242, 1087, 1010, 790 $cm.^{-1}$ (KBr).

Anal. Calcd. for $C_{27}H_{48}OS$ (420.716): C, 77.07; H, 11.50; S, 7.62. Found: C, 76.72; H, 11.37; S, 7.51.

Base treatment of Desyl Benzylxanthate (XV). - To dexyl benzylxanthate (3.8 g., 10 mmoles) in 250 ml. of dioxane and 30 ml. of chloroform (to completely dissolve the solid) was added 60 ml. of 1.5 N aqueous potassium hydroxide (90 mmoles), and this reaction mixture was stirred at room temperature for 2 hr. with a stream of nitrogen gas bubbled through the solution. After this

time, 66 ml. of 5% hydrochloric acid (92.4 mmoles) and 300 ml. of water were added and the mixture extracted with ether. The ether layer was washed well with water, dried over anhydrous magnesium sulfate and evaporated. The resultant oil was passed through a short column of silica gel.

Benzene and benzene-chloroform (1:1) eluted 926 mg. (34%) of cis-stilbene-α(S),α'(O)-dithiocarbonate (XVI). One crystallization from acetone-hexane gave pale yellow, light-sensitive crystals melting at 132-133°; ν_{max} 1181, 1175, 1060, 764, 755, 690, 686, 676, 648, 550 cm.$^{-1}$ (KBr); log ε^{max}_{327} 4.41, log ε^{min}_{273} 3.72, log ε^{max}_{225} 4.35, log ε^{min}_{215} 4.10 (95% ethanol). Mass Spectrum: m/e 270 (M^+), m/e 165 (M-105), m/e 121 ($C_6H_5CS^+$), m/e 105 ($C_6H_5CO^+$), m/e 77 ($C_6H_5^+$).

Anal. Calcd. for $C_{15}H_{10}OS_2$ (270.36): C, 66.63; H, 3.73; S, 23.72. Found: C, 66.62; H, 3.87; S, 23.48.

Chloroform and chloroform-ether (1:1) eluted 1.5 g. of a mixture of what is probably α-keto thiol and the corresponding disulfide. The yield was 55%, based on thiol. This mixture was not further investigated.

Base Treatment of Benzoin S-methyl xanthate (XX). - Benzoin S-methyl xanthate (110 mg., 0.364 mmole) was dissolved in 5 ml. of ether and to this solution was added a solution of 0.5 g. (8.9 mmoles) of potassium hydroxide in methanol. The solution was allowed to stand at room temperature for 45 min., during which time the solution exhibited a violet tinge on a yellow background. The violet color disappeared, leaving a yellow solution. This solution was added to water, ether, and enough hydrochloric acid to neutralize the base. The ether layer was washed well with water, dried over anhydrous magnesium sulfate and evaporated, leaving a yellow oil. Light yellow crystals of benzyl (XXI) were obtained from the oil by crystallization from n-pentane, 50 mg. (65%) m.p. 94-95°, mixture melting

point 94-96°. The mother liquor (20 mg.) was mainly benzil by chromatoplate. The theoretical yield of benzil is 76.5 mg.

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