(g) **Lactone.**—A chloroform solution (2 cc.) containing 0.138 g. of perbenzoic acid was added to 155 mg. of ketone 104, which promptly dissolved. The solution was let stand at 5–7° for 24 hr. and then at 25° for 18 hr., treated with water and ether and the ethereal layer washed with water and with bicarbonate solution, dried and evaporated. The residual oil, after attempted crystallization had failed, was refluxed for 1 hr. with 5 cc. of methanol and 1 cc. of Claisen alkali. The solution was diluted with water, extracted with ether, and the ether back-washed with 2 *N* sodium hydroxide solution. The combined aqueous solutions were acidified with hydrochloric acid at 25° and the precipitated gum recovered by extraction with ether. The washed and dried extract on evaporation gave 121 mg. of residue; a solution of this in methanol was cooled in a salt–ice-bath, and on scratching the lactone separated as a solid. Three crystallizations from methanol gave 25 mg. of needles, m.p. 89–90°, α_D +8.9° Chf (*c* 1.48), λ 5.80, 8.8, 11.15 μ.

Anal. Calcd. for $C_{27}H_{44}O_4$ (432.62): C, 74.95; H, 10.25. Found: C, 74.87; H, 10.36.

In another experiment the aqueous alkaline solution was cooled to 0°, acidified with cold (0°) 2 *N* sulfuric acid, and the precipitated gum extracted rapidly with chilled ether. The ethereal solution was washed twice with ice-water and poured into an ethereal solution of diazomethane. The solution was dried and evaporated and the residue chromatographed. The only solid product was the lactone, m.p. and mixed m.p. 89–90°.

(h) **Resistance to Acid.**—A solution of 100 mg. of ketone 104 in 5.6 cc. of methanol and 0.3 cc. of 95% sulfuric acid was refluxed for 3 hr. Crystallization of the product from methanol gave 85 mg. of unchanged starting material. A mixture of 90 mg. of ketone, 22 cc. of methanol, and 1 cc. of 95% sulfuric acid was refluxed for 16 hr., but only unchanged ketone 104 was recovered (70 mg.).

(i) **Action of Hypobromite.**—Four cc. of a solution of 3 g. of bromine in 44.4 cc. of 4% sodium hydroxide was added to a cold solution of 100 mg. of ketone 104 in 30 cc. of dioxane and 3 cc. of pyridine and the solution was let stand 1 hr. at 7–9° and 48 hr. at 25°. No acidic product was formed.

(j) **Action of Bromine.**—Ketone 104 did not absorb bromine in carbon tetrachloride or in acetic acid, with or without addition of dry hydrogen bromide.

(k) **Action of Girard's Reagent T.**—A mixture of 88 mg. of ketone 104, 6 cc. of methanol, 73 mg. of reagent and 0.1 cc. of acetic acid was refluxed for one-half hour, cooled, diluted with water and extracted with ether. The washed and dried ethereal extract furnished 32 mg. of unchanged ketone and the rest was recovered from the hydrolyzed aqueous layer. In another experiment 60 mg. of ketone was treated similarly with reagent (70 mg.) in methanol (25 cc.)–acetic acid (0.1 cc.) at 25° for 2 hr.; 55 mg. of unreacted ketone 104 was recovered from the ether phase.

(l) **Action of Phosphorus Oxychloride.**—A mixture of 105 mg. of ketone 104, 0.4 cc. of phosphorus oxychloride and 1 cc. of pyridine was let stand at 25° for 48 hr.; 80 mg. of unchanged ketone was recovered.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Chromic Acid Oxidation of Epicholesteryl Acetate

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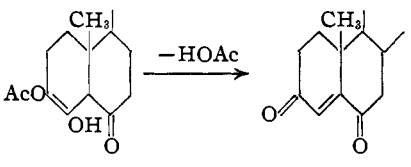
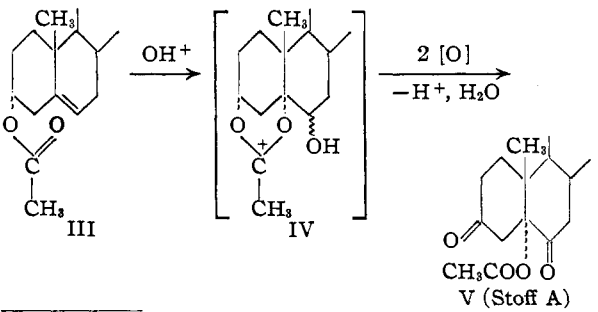
One of two products obtained by Windaus and Naggatz in 1939, by chromic acid oxidation of epicholesteryl acetate, has been identified as cholestane-3,6-dione-5α-ol 5-acetate (V). It is formed by oxidation in propionic acid as well as in acetic acid solution and hence results from an intramolecular $C_3 \rightarrow C_5$ acyl migration, probably involving a cyclic acetal (IV).

Windaus and Naggatz[2] investigated the oxidation of epicholesteryl acetate with chromic acid in acetic acid solution as the first step in the synthesis of 7-dehydroepicholesterol. They noted that the principal product, the expected 7-ketone, is distinguished from the 3β-acetoxy epimer by more ready elimination of acetic acid with formation of $\Delta^{3,5}$-cholestadiene-7-one; it is of interest that probably the 3α-acetoxy group is polar whereas the 3β-acetoxy group is equatorial. A second oxidation product isolated in 14% yield was designated "Stoff A" and shown to have the empirical formula $C_{29}H_{46}O_4$. It was characterized merely as being transparent to ultraviolet light and as convertible by chromatography on alumina or by treatment with alcoholic alkali into Δ^4-cholestene-3,6-dione (II), and the possible formulation I was suggested very tentatively and with evident lack of conviction.



I (Stoff A?) II

In a reinvestigation of this secondary oxidation product we were able to confirm all the observations of Windaus and Naggatz. The infrared spectrum provided further evidence of the presence of an acetate (5.76, 8.0 μ) and a carbonyl group (5.81 μ) but showed no band in the hydroxyl region. The only plausible way in which the elements of acetic acid can be considered to be added to Δ^4-cholestene-3,6-dione without producing a hydroxyl group is that leading to cholestane-3,6-dione-5α-ol-5-acetate (V). This substance was prepared by Hattori[3] by chromic acid oxidation of cholestane-3β,5α,6β-triol 5-acetate and the constants agree well with those of "Stoff A." Direct comparison of samples prepared in the two ways proved their identity.



III IV V (Stoff A)

(1) This work was conducted under a scholarship granted by the National Research Council of Canada.

(2) A. Windaus and J. Naggatz, *Ann.*, **542**, 204 (1939).

(3) J. Hattori, *J. Pharm. Soc. Japan*, **59**, 411 (1939); English abstract, *ibid.*, **59**, 129 (1939).

The acetyl group that appears on the oxygen at C_5 could conceivably be that originally at C_3, or it could result from solvolysis (acetic acid) of an intermediate 5,6-oxide, a reaction postulated[4] to account for the formation of cholestane-3β,5α-diol-6-one 3,5-diacetate on chromic acid oxidation of cholesteryl acetate.[5] In the case at hand such a process is ruled out by the observation that "Stoff A" (V) is formed in about the same yield when the oxidation of III is conducted in propionic acid rather than in acetic acid. Evidently an intramolecular acyl migration is involved. Comparable acyl migrations are well known. Thus the 3-acetate of Δ^5-cholestene-3β,4β-diol rearranges to the 4-acetate, probably through the cyclic acetal derivative.[6] Plattner and Lang[7] converted cholestane-3β,5α-diol 5-acetate into epicholesteryl acetate by reaction with *p*-toluenesulfonyl chloride in pyridine and postulated that the acyl migration and attending inversion at C_3 results through intermediate formation of a 3α,5α-cycloacetal derivative; a related carbonate derivative has been made by reaction of cholestane-3α,5α-diol with phosgene.[8] The reverse $C_3 \rightarrow C_5$ migration now reported can be considered to proceed by attack of OH^+ at the 5,6-double bond of epicholesteryl acetate with concerted formation of the cyclic acetal derivative IV, followed by oxidative fission to cholestane-3,6-dione-5α-ol 5-acetate (V). An analogous rearrangement in the partial dichromate oxidation of cholesterol has been reported in a recent paper from this Laboratory.[9]

Experimental[10]

Epicholesteryl acetate (m.p. 85.6°, α_D −11° Chf (*c* 1.54)) was initially prepared by reduction of cholesterol α-oxide with lithium aluminum hydride to cholestane-3β,5α-diol[11] and solvolysis of the 3-mesyl-5-acetyl derivative of the diol.[8] Later batches were made more conveniently by acetylation of epicholesterol prepared by partial oxidation of cholesterol.[9]

Cholestane-3,6-dione-5α-ol 5-Acetate (V).—A solution of 5 g. of epicholesteryl acetate (0.0117 mole) in 50 cc. of acetic acid was stirred at 50° and this temperature was maintained during the addition, in 1 hr., of a solution of 3.5 g. of chromic anhydride (4.5 oxygen equivalents) in 5 cc. of 50% acetic acid. The mixture was let stand at 25° for 3 hr., diluted with water, and extracted with ether. The extract was washed neutral, dried and evaporated, and the solid residue crystallized from 30 cc. of methanol. The crystallizate (1.57 g., m.p. 144–149°) consisted largely of the acetoxydione V. Several crystallizations from methanol gave colorless needles, m.p. 165–166° (lit.[2] 163°), α_D +3.7° Chf (*c* 1.46), λ^{Chf} 5.76, 5.81, 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.81; H, 10.04.

When 2 g. of epicholesteryl acetate was oxidized by the same procedure in propionic solution processing of the reaction mixture was rendered difficult by the marked formation of reduced (purple) compounds of chromium. After an initial crystallization from petroleum ether, repeated crystallization from methanol (norit) gave, in about 12% yield, a product, m.p. 165–166°, α_D +4.1° Chf (*c* 1.52), that showed no depression in m.p. when mixed with the sample of V prepared by oxidation in acetic acid solution.

Conversion of V into Δ^4-cholestene-3,6-dione was accomplished by brief treatment with Claisen alkali (76% yield) and by chromatography on acid-washed alumina (quantitative yield).

For preparation of a comparison sample of cholestane-3,6-dione-5α-ol 5-acetate, cholestane-3β,5α,6β-triol[12] was converted to the triacetate (m.p. 149–150°, α_D −34.6° Chf) under catalysis by *p*-toluenesulfonic acid (yield 86%), essentially according to Davis and Petrow[13] and the triacetate was partially hydrolyzed to the 5-monoacetate[3] by boiling 600 mg. of material in 20 cc. of methanol with 1 cc. of Claisen alkali for 30 min. The product, collected after acidification and crystallized from methanol, gave 400 mg. (79%) of cholestane-3β,5α,6β-triol 5-acetate, m.p. 168–169°, α_D +2.5° Chf (*c* 1.51). A solution of 500 mg. of the 5-acetate in 20 cc. of acetic acid was treated, with cooling, with 500 mg. of chromic anhydride in 2 cc. of 50% acetic acid and let stand at 25° for 2 hr. A first crystallization from methanol gave 270 mg. (55%) of cholestane-3,6-dione-5α-ol 5-acetate (V) as white needles, m.p. 162–163°. Further crystallizations gave material of m.p. 165–166°, α_D +3.7° Chf (*c* 1.50), λ^{Chf} 3.76, 5.81, 8.0 μ; no depression in m.p. on admixture with the sample prepared from epicholesteryl acetate.

CAMBRIDGE, MASSACHUSETTS

(4) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Corp., New York, N. Y., 1949, pp. 231–232.

(5) Fr. Schenck, *Z. physiol. Chem.*, **243**, 119 (1936).

(6) V. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 135 (1943); M. F. C. Paige, *ibid.*, 437 (1943).

(7) Pl. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944).

(8) Pl. A. Plattner, A. Fürst, F. Koller and W. Lang, *ibid.*, **31**, 1455 (1948).

(9) L. F. Fieser, THIS JOURNAL, **75**, 4377 (1953).

(10) All melting points are corrected.

(11) Pl. A. Plattner, H. Heusser and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949).

(12) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3938 (1949).

(13) M. Davis and V. Petrow, *J. Chem. Soc.*, 2536 (1949).