aqueous layer extracted with carbon tetrachloride. The combined carbon tetrachloride solution was evaporated under reduced pressure. The residue was an amber oil (43 g.) which solidified upon standing in the cold. The solid after recrystallization from petroleum ether weighed 37 g.

3-Trichloromethanesulfenyl-5-benzylidenethiazolidine-2,4-dione. Method III.—A mixture of the potassium salt of 5-benzylidenethiazolidine-2,4-dione[2c] (20 g.), trichloromethanesulfenyl chloride (15.3 g.) and carbon tetrachloride (150 ml.) was stirred for three hours. The solid was collected and recrystallized from a mixture of acetone and methanol. The 3-trichloromethanesulfenyl-5-benzylidenethiazolidine-2,4-dione thus obtained weighed 21 g.

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RESEARCH LABORATORIES
ROHM AND HAAS COMPANY
PHILADELPHIA 37, PENNA.

Cholesterol and Companions. VII. Steroid Dibromides

BY LOUIS F. FIESER

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Among many reported instances of the bromination of Δ^5-stenoids, occasional reference has been made to the use of pyridine[1] or sodium acetate[2] as a buffer to neutralize traces of hydrogen bromide. Being unaware of any prior comparison, I wish to report that whereas bromination of cholesterol (150-g. lots) in ether by addition of a solution of bromine in acetic acid (Windaus[3] procedure) gave the dibromide (as the acetic acid complex) in 72–74% yield, the yield rose to 84% on addition of 0.14 equivalent of sodium acetate.

Windaus' method[3] of debromination with zinc dust in boiling acetic acid is applicable, with some limitations,[4,5] to stenyl acetate dibromides[6] and to the conversion of 5,6-dibromo-3-ketones into Δ^4-stene-3-ones,[3] but not to free sterol dibromides because of the ready acetylation of sterols in hot acetic acid.[7] Since newer methods of debromination utilizing sodium iodide,[8] ferrous chloride[9] or chromous chloride[5] did not seem well adapted to rapid, large-scale operation, the Windaus method was reinvestigated and a simple modification found that eliminates the difficulties: a suspension of the dibromide in ether containing a small amount of acetic acid is stirred at room temperature and zinc dust is added. A vigorous, exothermic reaction reminiscent of the formation of a Grignard reagent sets in and is soon complete; the yield of cholesterol from the dibromide is 93%. This material is free from cholestanol, 7-dehydrocholesterol, and lathosterol[7]; the first-crop material from methanol is free also from cerebrosterol[10] and from 25-hydroxycholesterol, a product of autoxidation that has been found present in old samples.

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The new procedure is also applicable to the debromination of 5,6-dibromocholestanone, obtainable on a large scale in 96.5% yield by oxidation of cholesterol dibromide with sodium dichromate in place of chromic acid.[11,12] The reaction with zinc dust in ether–acetic acid proceeds rapidly at 15–20° and Δ^5-cholestene-3-one of high purity is obtained in 88% yield. Debromination to the Δ^5-stenone with zinc dust and boiling ethanol[11] proceeds satisfactorily on a small scale but on a large scale gives material of inferior quality.

The three steps leading to Δ^5-cholestene-3-one seemed so satisfactory for preparative purposes that the further conversion to Δ^4-cholestene-3-one was explored. Isomerization catalyzed by a mineral acid or a base, while applicable on a micro scale,[11] gave inferior material as applied to 100-g. lots. However, oxalic acid in ethanol effected isomerization smoothly and afforded in 98% yield cholestenone corresponding in melting point (81–82°) and extinction coefficient to material purified by chromatography[13]; the over-all yield from cholesterol is 69%. Because of the high purity of the product and since all the steps from cholesterol can be completed in a few hours, this route rivals direct Oppenauer oxidation, which affords cholestenone, m.p. 77–79°, in 70–81% yield.[14]

Experimental

Cholesterol Dibromide.—One hundred and fifty grams of commercial cholesterol was dissolved in 1 l. of absolute ether by brief boiling in a 4-l. beaker, the solution was cooled to 25°, and a solution of 5 g. of anhydrous sodium acetate and 68 g. of bromine in 600 cc. of acetic acid was added. The solution turned yellow and a stiff paste of dibromide promptly resulted. The mixture was cooled to 20° and the product collected and washed with acetic acid (500 cc.) until the filtrate was colorless. A second crop of satisfactory material was obtained by adding 800 cc. of water to the combined yellow filtrate and washings, filtering the precipitate and washing it free of yellow mother liquor with acetic acid. When spread out on a paper and let dry in a hood at room temperature overnight, the material reaches a weight unchanged by drying for another day or two and appears from the infrared spectrum to be a 1:1 acetic acid complex, and percentage yields are calculated on this basis. Yields obtained in the first and second crops are: 182.4, 14.7 g.; 171.5, 25.2 g.; total yield 197.1, 196.7 g. (84%).

The infrared spectrum of the air-dried dibromide in chloroform resembles that of the 2:1 cholesterol–oxalic acid complex. In each case the band in the hydroxyl region is minor and shifted to about 3.0 μ, bands ordinarily associated with free carboxyl group and ester groups are absent, and a prominent band at 5.79–5.81 μ and a less intense band at 5.6–5.7 μ probably are characteristic of a carbonyl group in this particular type of acid–alcohol complex.

Cholesterol already purified through the dibromide afforded dibromide in only slightly higher yield (85%). In numerous earlier brominations made in exactly the same way but without addition of the small amount of sodium acetate the yield in the first crop was only 72–74% and the second crop contained much unbrominated material. Doubling of the amount of sodium acetate specified produced no change in the result.

Cholesterol from the Dibromide.—The acetic acid–moist dibromide from 150 g. of cholesterol was suspended in 1.2 l. of ether in a flask equipped with a stirrer and with provision for ice cooling when required. Fresh zinc dust (40 g.) was added in the course of 5 min. The first 5–10 g. was added without cooling; when the reaction had started, as evi-

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(13) E. R. H. Jones, P. A. Wilkinson and R. H. Kerlogue, *J. Chem. Soc.*, 392 (1942).
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denced by solution of part of the dibromide, the cooling bath was raised during the remainder of the addition. At the end, the ice-bath was removed and the mixture, which soon set to a heavy paste of white solid,[15] was stirred for 15 min. longer. Then 50 cc. of water was added to dissolve the zinc salt and the ethereal solution was decanted into a separatory funnel and washed with 400 cc. of water containing 25 cc. of 36% hydrochloric acid. After three more washings with 400 cc. of water, the solution was shaken with 300 cc. of water and 150 cc. of 25% sodium hydroxide solution and the ether layer tested to make sure it contained no trace of acetic acid (which readily acetylates the sterol during evaporation). The solution was then dried, evaporated to about 600 cc., 600 cc. of methanol was added, and the solution boiled down to the point of incipient crystallization (about 1 l.). After cooling (4°), the main crop of purified cholesterol was collected and dried: 108.4 g., m.p. 149.5–150°; a second crop of 8.4 g., m.p. 148–149°, was obtained after evaporation to a volume of 250 cc.; total yield 116.8 g. (93%). The residual mother liquor afforded about 4 g. of material containing bromine not removed by repetition of the treatment with zinc dust. If air-dried dibromide is used, 25 cc. of acetic acid should be added to the ethereal suspension before addition of zinc.

5α,6β-Dibromocholestane-3-one.—The moist dibromide from 150 g. of cholesterol was suspended in 2 l. of acetic acid in a 5-l. flask equipped with a stirrer and mounted over a bucket of ice and water that could later be raised, and a solution, preheated to 90°, of 80 g. of sodium dichromate dihydrate in 2 l. of acetic acid was poured into the stirred suspension (at 25°). The temperature of the mixture reached 55–58° during the oxidation and the solid all dissolved in 3–4 min. After another 2 min. the ice bucket was raised so that the flask was completely immersed and the stirrer was stopped for 10 min. to allow the dibromoketone to separate in easily filterable crystals. With stirring resumed, the temperature was brought to 25° and then, after addition of 400 cc. of water, to 15°. The product was collected, washed with methanol until the filtrate was colorless (500–600 cc.) and the white crystals, m.p. 73–75° dec., $[\alpha]^{25}D$ −46.8° Chf (*c* 2.11) were either used while still moist or dried in a dark cupboard at room temperature; yield 170.9 g. (96.5% in the oxidation, 81% from cholesterol). Butenandt[11] and Inhoffen[12] report m.p. (dec.) 80° and 68–69°.

Δ⁵-Cholestene-3-one.—The methanol-moist dibromocholestanone from 150 g. of cholesterol was covered with 2 l. of ether, 25 cc. of acetic acid was added, and the mixture stirred mechanically in an ice-bath and the temperature lowered to 15°. Then 40 g. of fresh zinc dust was added in portions in the course of 5 min. with maintenance of a temperature of 15–20° by cooling. When the exothermic reaction was over, the ice-bath was removed and stirring continued for 10 min. Then 70 cc. of pyridine was added and the resulting suspension of white complex stirred briefly; the solution was then filtered by suction and the filter cake washed well with ether. The colorless filtrate was washed three times with water and once with 600 cc. of 5% bicarbonate solution (to remove a trace of acetic acid), dried, and evaporated to a volume of 1 l. After addition of 500 cc. of methanol, evaporation was continued to a volume of 1.2 l. and the product let crystallize. It separated in large, pure white prisms, m.p. 126–129° (camphor-like), $[\alpha]D$ −2.5° Chf (*c* 2.03), no selective absorption at 242 mμ. The yield in the first crop was 87–94 g., and concentration of the mother liquor afforded 12–19 g. more of colorless material melting in the range 118–124° and suitable for conversion to the conjugated ketone; total yield 106 g. (88%, 71% from cholesterol).

Debromination with zinc and ethanol according to Butenandt and Schmidt-Thomé[11] when conducted on the same scale as above afforded crude Δ⁵-cholestene-3-one in 81–85% yield, but the material melted at 116–120°. Chromatography of the ethanolic mother liquor afforded Δ⁴-cholestene-3-one, Δ⁴-cholestene-3,6-dione and Δ⁴-cholestene-6β-ol-3-one; the last two products must be derived from cholesterol formed from the dibromide during the oxidation.

Δ⁴-Cholestene-3-one.—One hundred grams of Δ⁵-cholestene-3-one and 10 g. of anhydrous oxalic acid were dissolved in 800 cc. of 95% ethanol and the colorless solution was warmed for 10 min. on the steam-bath and then let cool to room temperature and seeded. The main crop of conjugated ketone (91.1 g.) separated as large, colorless prismatic needles, m.p. 81–82°, $[\alpha]D$ +92.0° Chf (*c* 2.01), λ^{EtOH} 242 mμ (17,000); constants reported[13] for material purified by chromatography are: m.p. 81–82°, λ^{EtOH} 240.5 mμ (18,000). Further crops were obtained first by concentration of the mother liquor and then by dilution with water, and these on recrystallization gave 6.8 g. of colorless product, m.p. 81–82°; total yield 97.9% (69% from cholesterol).

Isomerization of Δ⁵-cholestene-3-one in ethanol with either hydrochloric acid or sodium hydroxide (followed by neutralization of the yellow enolate solution with acetic acid) proved unsatisfactory on a large scale since a permanent yellow color developed and the first-crop material was yellowish and melted at 78–80°.

CHEMICAL LABORATORY OF HARVARD UNIVERSITY
CAMBRIDGE, MASS.

(15) This solid, m.p. about 170° dec., contains zinc and affords cholesterol on crystallization from methanol or acetone; it was not obtained in a form suitable for analysis.

Oxidation of 10-Acyl- and 10-Alkylphenothiazines

BY HENRY GILMAN AND R. DAVID NELSON

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A number of acid chlorides react readily with phenothiazine in pyridine to give 10-substituted phenothiazines.[1] Later reports[2] have shown that phenothiazine, and some of its nuclearly substituted derivatives, react with various haloacyl halides when heated in refluxing benzene or toluene to give the corresponding 10-haloacylphenothiazines in good yield. In this work, the 10-acylphenothiazines (Table I) were prepared by allowing the acid chloride to react with phenothiazine in the presence of dioxane and sodium carbonate.

A variety of oxidizing agents has been used to oxidize the sulfur of a number of phenothiazine derivatives to the sulfoxide or the sulfone. Those which oxidized the sulfur to the sulfoxide were potassium permanganate,[3,4] 30% hydrogen peroxide in ethanol,[5] sodium nitrite[6] and nitric acid.[6] In the latter case nitration also resulted. The sulfur has been oxidized to the sulfone by potassium permanganate,[4] 30% hydrogen peroxide in glacial acetic acid[7,8] and hypochlorous acid.[8] This note includes additional studies made on the oxidation of the sulfur of the phenothiazine nucleus.

The reaction of concentrated nitric acid with 10-chloroacetylphenothiazine in glacial acetic acid gave 3-nitrophenothiazine-5-oxide (I) and 10-chloroacetylphenothiazine-5-oxide but apparently no 3-nitro derivative of the latter compound. It appears that the acyl derivative was first oxidized by nitric acid to give the monoxide and that this reaction was then followed by hydrolysis and nitration resulting in the formation of I. Previous reactions using nitric acid and phenothiazine, or some of its derivatives, gave the corresponding

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