[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Selenium Dioxide Oxidation of Methyl Δ^3-Cholenate

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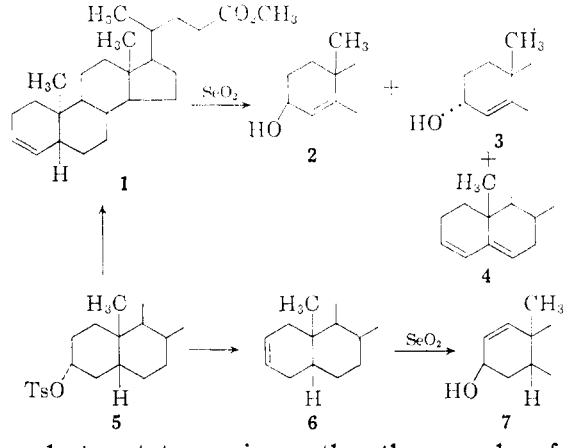
RECEIVED SEPTEMBER 28, 1959

Selenium dioxide oxidation of methyl Δ^3-cholenate gives about equal amounts of the 3β- and 3α-hydroxy-Δ^4-cholenates **2** and **3**, along with the $\Delta^{3,5}$-diene **4**, obtained also by dehydration of both allylic alcohols. A sample of starting material prepared from the tosylate of methyl lithocholate also gave the 3β-hydroxy-Δ^1-cholenate **7**, shown to be derived from about 25% of methyl Δ^2-cholenate present.

As the major product of pyrolysis of lithocholic acid, Wieland and Weyland[2] obtained an acid which could be purified by regeneration from either of two dibromides and which was later shown to be Δ^3-cholenic acid by an unequivocal synthesis from methyl 3α- or 3β-hydroxy-4β-bromocholanate[3,4] and by oxidation to lithobilianic acid.[5] Wieland, Kraus, Keller and Ottawa[6] studied the oxidation of the unpurified free acid prepared by pyrolysis and reported isolation of three products which, however, were characterized only by melting point as follows: two hydroxycholenic acids, m.p. 144–147° and 186–188°, and a dihydroxycholenic acid, m.p. 248°. We were interested in the reaction in connection with a study of the selenium dioxide oxidation of Δ^7-stenols,[7] but elected to use the methyl ester rather than the free acid. The first experiments utilized methyl Δ^3-cholenate prepared conveniently according to Chang, *et al.*,[8] by the action of lutidine on the tosylate of methyl lithocholate. Use of a large excess of selenium dioxide as in the Wieland procedure led to intractable mixtures, and under the mild conditions used for oxidation of Δ^7-stenols the reaction was too slow to be serviceable, but oxidation in acetic acid at room temperature for 35 hr. gave satisfactory, reproducible results.

The product, an evident mixture, was chromatographed after acetylation. Early fractions (9:1 petroleum ether–benzene) afforded starting material and then (4:1 solvent mixture) a substance characterized as methyl $\Delta^{3,5}$-choladienate because it exhibits the three-banded, high-intensity ultraviolet absorption spectrum characteristic of steroid $\Delta^{3,5}$-dienes.[9] The strong levorotation (α_D −136° Chf) is also consistent with a $\Delta^{3,5}$-system. Since further conventional chromatography had seemed impracticable, the column was then stripped with benzene and the mixture recovered from the combined eluates was saponified; relatively strong alkali was used in order to minimize epimerization.[10] Further separation was then achieved by treatment with digitonin. The precipitable fractions recovered from the digitonide consisted essentially of two components, separable by fractional crystallization. They proved to be isomeric hydroxycholenic acids, m.p. 182 and 155°. A third hydroxycholenic acid, m.p. 170°, was isolated from the non-precipitable fraction by chromatography as the methyl ester acetate. All three acids are allylic, since the corresponding methyl esters are readily oxidized by manganese dioxide.[11] The isomer not precipitated by digitonin and one of the precipitable isomers, oxidized as esters, afforded methyl 3-keto-Δ^4-cholenate, identified by comparison with an authentic sample.[12] They are therefore the two 3-hydroxy-Δ^4-cholenic acids, the precipitable 3β-ol **2** and the non-precipitable 3α-ol **3**. In accordance with the observations of Mills,[13] the epimeric allylic alcohols differ in optical rotation by a large increment and the 3β-ol is the



less dextrorotatory epimer; thus the α_D values for the methyl ester acetates of **2** and **3** are +20.9° Chf and +178° Chf. The structures assigned have since been confirmed by an unambiguous synthesis.[14]

The two products evidently arise by allylic attack and allylic rearrangement, the pattern observed in the oxidation of Δ^7-stenols[7]; the epimers are formed in approximately equal amounts. The melting points of the free acids are not far from those reported by Wieland,[6] but no other constants are available for comparison.

The structure of the second digitonin-precipitable hydroxycholenic acid then remained for elucidation. Manganese dioxide oxidation of the methyl ester

(1) On leave (1957–1958) from the Department of Chemistry of the American University of Beirut, Beirut, Lebanon.

(2) H. Wieland and P. Weyland, *Z. physiol. Chem.*, **110**, 136 (1920).

(3) L. F. Fieser and R. Ettorre, THIS JOURNAL, **75**, 1700 (1953).

(4) K. Yamasaki, V. Rosnati, M. Fieser and L. F. Fieser, *ibid.*, **77**, 3308 (1955).

(5) S. Hara, *Pharm. Bull. (Japan)*, **3**, 67 (1955).

(6) H. Wieland, K. Kraus, H. Keller and H. Ottawa, *Z. physiol. Chem.*, **241**, 47 (1936).

(7) L. F. Fieser and G. Ourisson, THIS JOURNAL, **75**, 4404 (1953).

(8) F. C. Chang, A. Feldstein, J. R. Gray, G. S. McCaleb and D. H. Sprunt, *ibid.*, **79**, 2167 (1957).

(9) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(10) M. P. Balfe, J. Kenyon and C. E. Searle, *J. Chem. Soc.*, 380 (1951).

(11) F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, THIS JOURNAL, **77**, 4145 (1955).

(12) T. F. Gallagher and J. R. Xenos, *J. Biol. Chem.*, **165**, 365 (1946).

(13) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

(14) M. J. Haddadin and C. H. Issidorides, *J. Org. Chem.*, in press.

gave a $\Delta^{\alpha,\beta}$-ketone of λ231–232 mμ (9,000), which indicates that the chromophore is of the β-monosubstituted type. Attempted elimination of the carbonyl function by desulfurization of the ethylenethioketal gave an intractable oil, but hydrogenation of the methyl ester proceeded smoothly to give a saturated keto ester identified as methyl 3-ketocholanate. The unsaturated ketone is therefore methyl 3-keto-Δ^1-cholenate, and the oxidation product, since it is digitonin-precipitable, is 3β-hydroxy-Δ^1-cholenic acid (**7**). Since this substance could hardly arise from methyl Δ^3-cholenate, it must have come from some of the Δ^2-isomer **6** present in the starting material prepared by the tosylate procedure. Since the Δ^2-isomer as such is not available, it seemed desirable to repeat the oxidation with starting material of assured purity prepared by the lengthier process of Fieser and Ettorre.[3] We are indebted to Naomi Levy for preparation of intermediates and to Toshio Goto for completing the preparative work and investigating the selenium dioxide oxidation. On chromatography of the acetylated mixture, he isolated the 3α- and 3β-acetoxy esters corresponding to **2** and **3** and the diene **4**, and examination of all mother liquors established the absence of the derivative of 3β-hydroxy-Δ^1-cholenic acid (**7**). The samples of methyl Δ^3-cholenate prepared by the tosylate method (A) and by the Fieser–Ettorre method (B), as well as a sample (C) prepared by pyrolysis of methyl lithocholate 3-benzoate were indistinguishable in melting point, but on examination of the infrared spectra we noted that samples A and C show bands at 14.70 and 15.05 μ, whereas sample B shows only the band at 14.70 μ (Fig. 1) . Both bands are characteristic of *cis*-disubstituted double bonds, and that at 15.05 μ is evidently due to the Δ^2-isomer. On the assumption that sample B is pure, calculation from the relative intensities of the band at 14.70 μ indicates that samples A and C contained 25 and 30%, respectively, of methyl Δ^2-cholenate.

Acknowledgments.—This work was supported by grants from the National Cancer Institute of the National Institutes of Health (CY 1696 Endo), the National Science Foundation, Research Corporation, and the Higgins Fund of Harvard University.

Experimental[15]

Methyl Δ^3-Cholenate, Sample A.—A solution of 100 g. of lithocholic acid in 1 l. of methanol containing 10 ml. of concd. hydrochloric acid was refluxed for 25 min., and the hot solution was filtered and let stand overnight for crystallization at 25° and then cooled to −2°. A first crop of colorless methyl lithocholate (83.0 g.) melted at 126.5–128°, unchanged on recrystallization; lit.: m.p. 129–130°,[16] 125–127°,[3] 125–127.5°.[8] The combined mother liquor and washings was neutralized with sodium bicarbonate, filtered and concentrated and gave a second (16.3 g.) and third crop (2.6 g.), both melting at 126–128°. Conversion to **methyl 3α-tosyloxycholanate** was accomplished[8] by adding 1.1 equivalents of *p*-toluenesulfonyl chloride to a solution of methyl lithocholate in dry pyridine[17] at 0°, letting the solution stand overnight at 0–3°, and pouring it onto ice with stirring. The solid product was washed with cold, dilute hydrochloric acid and with water, dried, and three crystallizations from 4:1 methanol–acetone gave plates, m.p. 119–121°, α_D + 37° Chf (*c* 2.16); lit.: 120–121.5°,[8] 110–112°,[18] α_D + 35°.[8]

Anal. Calcd. for $C_{32}H_{48}O_5S$ (544.75): C, 70.56; H, 8.88; S, 5.9. Found: C, 70.53; H, 9.09; S, 5.4.

Dehydrotosylation was accomplished according to Chang, *et al.*,[8] by refluxing the tosylate with lutidine for 3 hr. The resulting methyl Δ^3-cholenate was eluted from an alumina column with 9:1 petroleum ether–benzene and crystallized from methanol; m.p. 73.5–74.5°, α_D +18° Chf (*c* 2.3); lit.[8] m.p. 74.5–75°, α_D +17° Chf.

Anal. Calcd. for $C_{25}H_{40}O_2$ (372.57): C, 80.59; H, 10.82. Found: C, 80.65; H, 11.00.

Oxidation of Methyl Δ^3-Cholenate A.—A solution of 5 g. of methyl Δ^3-cholenate in 55 ml. of acetic acid was treated with a solution of 1.31 g. of selenium dioxide in 3.7 ml. of water diluted with 25 ml. of acetic acid. The mixture was stirred at 25–28° for 35 hr., diluted with 100 ml. of ether to facilitate filtration, filtered, diluted with water and the red filtrate was extracted with ether. The extract was washed with sodium carbonate solution, dried, stirred with precipitated silver[7] for 3 hr. (light yellow) and evaporated. The residue was treated with 60 ml. of pyridine and 30 ml. of acetic anhydride, and after standing overnight at room temperature the mixture was stirred onto ice and the solid eventually obtained was washed with water and dried to constant weight (5.1 g.). The solid was chromatographed on 150 g. of alumina and the column eluted with 80-ml. portions of solvent. Fractions 2-6, eluted by petroleum ether and 9:1 petroleum ether—benzene, solidified when rubbed with

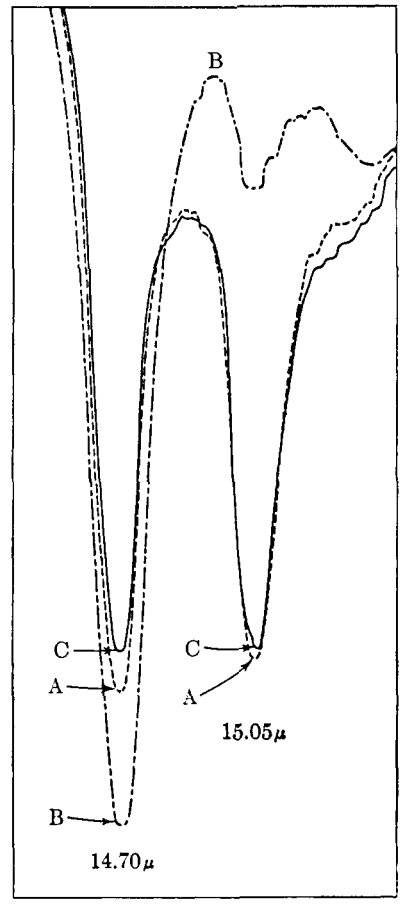


Fig. 1.—Infrared spectra of methyl Δ^3-cholenate: A, tosylate method; B, Fieser–Ettorre method; C, pyrolysis.

(15) Melting points are uncorrected. Infrared spectra were determined with a Perkin–Elmer model 21 spectrophotometer. Rotations, rounded off to the nearest integer, were measured at 23–27°. The alumina used for chromatography was Woelm grade 1, to which 3% of water was added.

(16) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

(17) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(18) J. C. Babcock and L. F. Fieser, THIS JOURNAL, **74**, 5472 (1952).

methanol and on two crystallizations gave a small amount of starting material (mixed m.p., infrared. Fractions 7–11 (9:1 to 8:2) solidified slowly on standing and on two crystallizations from methanol afforded 180 mg. of **methyl $\Delta^{3,5}$ choladienate**, m.p. 95–97°. On further crystallization the substance formed needles, m.p. 96.5–98°, α_D −136° Chf (*c* 0.9); λ^{MeOH} 227.5, 234.5, 243 mμ (20, 200; 21,700; 14,000); positive Rosenheim reaction.[19]

Anal. Calcd. for $C_{25}H_{38}O_2$ (370.55): C, 81.03; H, 10.34. Found: C, 81.00; H, 10.46.

An identical ester (mixed m.p. ultraviolet) was obtained from 3β-hydroxy-Δ⁴-cholenic acid (35 mg.) by esterification with diazomethane and refluxing the ester for 2 hr. with 15 ml. of methanol containing 0.06 ml. of concd. hydrochloric acid. Two crystallizations from methanol gave needles, m.p. 95–96.5°, α_D −124° Chf (*c* 0.7). 3α-Hydroxy-Δ⁴-cholenic acid on similar treatment gave the same product.

On the basis of observations made in earlier runs, the column was then eluted exhaustively with 1:1 petroleum ether–benzene and finally benzene and the eluates were combined and evaporated and the residue (3.1 g.) was refluxed for 80 min. with 70 ml. of 2.5 *N* methanolic potassium hydroxide. After dilution and acidification of the cooled solution, ether extraction afforded a mixture of hydroxycholenic acids.

3β-Hydroxy-Δ⁴-cholenic Acid (2).—A solution of the above mixture in 200 ml. of 95% ethanol was treated with a hot solution of 12 g. of digitonin in 1 l. of 90% ethanol and the mixture was let stand for 24 hr. and then filtered. The digitonide which separated was extracted in a Soxhlet apparatus with ether for 1.25 hrs. and a solution of the material in 90 ml. of dry pyridine was diluted with 500 ml. of ether. The mixture was centrifuged and the precipitated digitonin washed several times with ether. The ether washings were combined and concentrated on the steam-bath and the bulk of the pyridine was removed by heating at 40° (1 mm.). For removal of traces of pyridine, the viscous oily residue was dissolved in ether and the solution washed with cold, dilute hydrochloric acid and then with water, dried and evaporated. Two crystallizations of the residue from ethyl acetate gave 620 mg. of 3β-hydroxy-Δ⁴-cholenic acid, m.p. 177–179° dec. The analytical sample, obtained by further crystallization from acetone and from ethyl acetate, melted at 180–182° dec., α_D +51° Di (*c* 0.9), positive Rosenheim reaction.

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.47; H, 10.19.

3β-Hydroxy-Δ¹-cholenic Acid (7).—The ethyl acetate mother liquor remaining from crystallization of 3β-hydroxy-Δ⁴-cholenic acid was evaporated to dryness under reduced pressure and three crystallizations from aqueous methanol gave thin plates (430 mg.), m.p. 169–170.5°, α_D +135° Di (*c* 0.8), positive Rosenheim reaction.

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.80; H, 10.33.

The methyl ester benzoate separated from methanol in hexagonal plates, m.p. 144–145.5°, α_D +188° Chf (*c* 1. 3).

Anal. Calcd. for $C_{32}H_{44}O_4$ (492.67): C, 78.01; H, 9.00. Found: C, 78.03; H, 9.08.

Methyl 3α-Acetoxy-Δ⁴-cholenate.—The mother liquor and washings fromp recipitation of the digitonide was evaporated to dryness under reduced pressure and the residue was extracted repeatedly with ether in the cold. The filtered extract was evaporated and the solid residue was esterified with diazomethane and acetylated. Chromatography on alumina (elution by 7:3 to 6:4 petroleum ether–benzene) followed by three crystallizations from methanol gave 580 mg. of acetate methyl ester as needles, m.p. 147–149°, α_D +178° Chf (*c* 1.1), positive Rosenheim reaction.

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.18; H, 10.06.

Saponification of the acetate methyl ester with 2.5 *N* methanolic potassium hydroxide followed by crystallization from ether–petroleum ether gave plates of **3α-hydroxy-Δ⁴-cholenic acid**, m.p. 154–155°, α_D +120° Chf (*c* 0.8).

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.92; H, 10.41.

(19) O. Rosenheim, *Biochem. J.*, **23**, 47 (1929); R. Schoenheimer and E. A. Evans, *J. Biol. Chem.*, **114**, 567 (1936).

Repeated crystallization of this allylic hydroxy acid from aqueous methanol gave feathery needles, m.p. 170–172°, of what appears to be the 3-methyl ether. The methyl ester resisted oxidation with manganese dioxide and the infrared spectrum showed no hydroxyl band but a strong band at 9.3–9.4 μ. Facile methylation of other steroid allylic aclohols has been reported.[7,20]

Methyl 3-Keto-Δ⁴-cholenate.[12,21]—Esterification of 3β-hydroxy-Δ⁴-cholenic acid with diazomethane and oxidation with specially prepared[11] manganese dioxide in chloroform for 3.5 hr. at room temperature gave the unsaturated keto ester in 72–75% yield. The ester crystallized from aqueous methanol in stout needles, m.p. 126–127°, α_D +87° Chf (*c* 1.3), λ^{MeOH} 241 mμ (16, 800); λ^{Chf} 5.77, 6.01, 6.19, 11.55 μ.[22] Mixed m.p. and infrared comparison with a sample kindly furnished by Dr. T. F. Gallagher indicated identity. 3α-Hydroxy-Δ⁴-cholenic acid on esterification and oxidation yielded the same product in 76% yield.

Methyl 3-Keto-Δ¹-cholenate.—3β-Hydroxy-Δ¹-cholenic acid was esterified and the ester oxidized with manganese dioxide and the product chromatographed on alumina. Elution with 8:2 to 7:3 petroleum ether–benzene gave material melting at 135–137° in 63% yield. Two crystallizations from aqueous methanol gave shiny needles, m.p. 138.5–139.5°, λ^{MeOH} 231–232 mμ (9,000); λ^{Chf} 5.78, 5.98 5.20 μ (no band at 11.5–11.6 μ).

Anal. Calcd. for $C_{25}H_{38}O_3$ (386.55): C, 77.67; H, 9.91. Found: C, 77.39; H, 10.05.

The keto ester was also obtained from the mixture of digitonin-precipitated 3β-ols by esterification and oxidation, followed by chromatography (controlled by the ultraviolet spectrum). The Δ¹-3-ketone is eluted by 8:2 petroleum ether–benzene, while the Δ⁴-3-ketone requires 7:3 to 6:4 solvent mixtures.

Hydrogenation of the unsaturated keto ester (85 mg.) with palladium–charcoal in ethanol and two crystallizations from petroleum ether gave flat needles of **methyl 3-ketocholanate**, m.p. 117.5–118.5°, undepressed by admixture with an authentic sample.[3]

Anal. Calcd. for $C_{25}H_{40}O_3$ (388.57): C, 77.27; H, 10.38. Found: C, 77.12; H, 10.35.

Experiments by Toshio Goto

Methyl Δ³-Cholenate. Sample B.—Difficulties were experienced in repeating some of the procedures as reported by Fieser and Ettorre,[3] and the following modifications are regarded as more satisfactory. A vigorously stirred solution of 5.73 g. of methyl 3-ketocholanate in 60 ml. of acetic acid was treated at room temperature with a solution of 1.5 ml. of 1 *N* hydrogen bromide in acetic acid followed by a solution of 2.4 g. of bromine and 1.2 g. of sodium acetate in 30 ml. of acetic acid, added dropwise in 5 min. The solution was then poured at once onto ice and extracted with ether. The extract was washed three times with water and once each with bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, and evaporated to about 15 ml. under vacuum. Crystals separating on cooling in a refrigerator were collected and washed with a little ether; crystallization of the crude product (4 g.) from acetone–methanol gave 3.15 g. (52%) of **methyl 4β-bromo-3-ketocholanate**, m.p. 95–100°, recrystallized 100.5–101°. A solution of 3 g. of this material in 30 ml. each of ether and methanol was cooled in an ice-bath, 200 mg. of sodium borohydride was added, and the mixture let stand at 0° for 2 hr. After addition of a few drops of acetic acid the solution was evaporated under vacuum, and the oily bromohydrin mixture was refluxed for 30 min. with 9 g. of zinc dust in 50 ml. of acetic acid. The solution was then decanted, diluted with water, extracted with ether, and the oily product when crystallized twice from 50-ml. portions of methanol gave 1.06 g. of needles of methyl Δ³-cholenate, m.p. 72–73; recrystallized, m.p. 75–77°, α_D +21.2° Chf. Chromatographed on 27 g. of alumina, 1.02 g. of oily mother liquor material afforded 2:1 petroleum ether–benzene eluates yielding 450 mg. of crystals which on crystallization from methanol gave nee-

(20) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1798 (1948).

(21) K. Takeda and J. Kawanami, *J. Biochem. Japan*, **40**, 477 (1953).

(22) The band at 11.55 μ is characteristic of Δ⁴-3-ketones; see K. Dobriner, E. R. Katzenellenbogen and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publishers, Inc., New York, N. Y., 1953.

dles, m.p. 72–73.5° (350 mg., total yield of 59% from the bromoketone).

Oxidation of Methyl Δ^3-Cholenate B.—Oxidation of 1.73 g. of ester was done exactly as before and the crude product was acetylated. The yellowish, glassy acetate mixture (2.05 g.) was then chromatographed on 50 g. of Merck alumina (87 50-ml. fractions). No starting material was encountered, but petroleum ether–benzene (2:1) eluates afforded 100 mg. of solid which on crystallization from methanol gave 70 mg. of plates of **methyl $\Delta^{3,5}$-choledienate**, m.p. 93–96°. The next crystalline fractions (2:1 and 15:10) gave 350 mg. of a mixture which on repeated crystallization gave 80 mg. of **methyl 3α-acetoxy-Δ^4-cholenate**, m.p. 148–150°, mixed m.p. 147–149°. Material recovered from the mother liquors was saponified and found to contain no digitonin-precipitable alcohol. Elution with 1:1 to 1:2 solvent mixtures afforded 260 mg. of material characterized by the infrared spectrum as essentially pure **methyl 3β-acetoxy-Δ^4-cholenate**. Crystallization from methanol gave leaflets (190 mg.), m.p. 142–148°, and the substance on further crystallization formed needles (120 mg.), m.p. 147.5–149°, α_D +20.9° (a mixture with the 3α-epimer melted at 118–132°).

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.51; H, 10.04.

Saponification of this methyl ester acetate and crystallization from methanol and then acetone gave prismatic needles of **3β-hydroxy-Δ^4-cholenic acid**, m.p. 174–176°, undepressed in m.p. on admixture with the above sample. The mother liquor material from crystallizations of the methyl ester acetate was saponified; the product precipitated by digitonin proved to be 3β-hydroxy-Δ^4-cholenic acid.

Benzene–ether eluates gave 230 mg. of an oil that gradually crystallized. Several crystallizations from methanol gave long needles, m.p. 157–159° (10 mg.); the analysis (C, 71.79; H, 8.94) suggests that the substance is a product of further oxidation.

Methyl Lithocholate 3-Benzoate (By Naomi Levy).—A solution of 2.2 g. of methyl lithocholate in 15 ml. of pyridine (dried over potassium hydroxide and distilled) was cooled in an ice-bath during dropwise addition of a solution of 1.3 g. of benzoyl chloride in 10 ml. of benzene. After standing overnight at room temperature, the mixture was worked up and the product crystallized from ethanol, m.p. 74–79°. Two further crystallizations raised the m.p. to 83–85°.

Anal. Calcd. for $C_{32}H_{46}O_4$ (494.69): C, 77.69; H, 9.37. Found: C, 78.00; H, 9.53.

This methyl ester benzoate (1 g.) was pyrolyzed in a sublimation apparatus heated in a Wood's metal-bath at 315–325° under evacuation by an oil-pump. After 1 hr. the white sublimate and oily residue were combined and extracted with ether, and the extract was washed with bicarbonate solution, dried, and evaporated. Chromatography afforded 400 mg. of **methyl Δ^3-cholenate C**, m.p. 69–70°.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Stereochemistry of B-Norcoprostane Derivatives[1]

BY TOSHIO GOTO[2]

RECEIVED SEPTEMBER 21, 1959

Reduction of B-norcoprostane-3,6-dione (**1**) with sodium borohydride affords a separable mixture of the 3α,6α- and 3α,6β-diol (**2**, **3**); hydrogenation gives the 3β,6β-diol (**4**). Diols **2** and **3** are both cyclized by benzenesulfonyl chloride in pyridine to the 3α,6α-oxide. That the reaction involves no rearrangement was established by conversion of the oxide to B-norcoprostane-6α-ol (**12**), prepared for comparison through intermediates **5** and **6**. Formation of the same 6α-ol by reduction of diol-**2** 3-tosylate (**7**) establishes the configuration of the diol at C_6. The configuration at C_3 follows from conversion of **1** to the 3α-ol,6-one **10**, which on borohydride reduction gave diol-**2** and on Wolff–Kishner reduction gave the known 3α-ol **11**. This evidence establishes that the dione **1** has the 5β-configuration. Experimental correlation of diol **3** with B-norcoprostane-3-one (**15**) by reactions which preclude an inversion at C_8 establishes the 8β-configuration at this center. The configurations of diols **3** and **4** follow from M_D and other considerations.

In 1937, Butenandt and Hausmann[3] encountered a new ketosecodioic acid and found that on brief refluxing with zinc and acetic acid it is cyclized to a diketone. Fieser[4] identified the acid as 6,7-seco-Δ^4-cholestene-3-one-6,7-dioic acid, named the product of cyclization the Butenandt diketone, and characterized it as a B-norstane-3,6-dione. Since the diketone has asymmetric centers at C_5 and C_8 adjacent to the carbonyl group at C_6, four stereoisomers are possible. In the absence of definitive evidence, Fieser provisionally formulated the compound as the B-norcoprostane-3,6-dione of normal 8β-configuration (**1**).

In an investigation of B-norcholesterol, Dauben and Fonken[5] concluded from various transformations that the stanol obtained by hydrogenation has the same configuration at C_5 as the Butenandt diketone. As a means of establishing whether the substances belong to the cholestane or the coprostane series, they investigated the reduction of the corresponding 3-ketone with lithium aluminum hydride and reported that the product is identical with the original 3β-ol. Since the ketone is unhindered, they assumed that the reaction affords the equatorial alcohol. Noting that a 3β-hydroxyl group is equatorial in the B-norcholestane series but axial in the B-norcoprostane series, they concluded that the alcohol is B-norcholestane-3β-ol. Djerassi, *et al.*,[6] however, found the rotatory dispersion curve of the norstane-3-one to resemble the curve of coprostanone rather than that of cholestanone and concluded that the substance is B-norcoprostane-3-one. Recently Dauben and coworkers[7] have resolved the seeming contradiction of evidence by the finding that the product of lithium aluminum hydride reduction is actually a mixture containing about 75% of the 3α-ol. They now regard the product of hydrogenation of B-norcholes-

(1) For a preliminary report of some of the results, see T. Goto and L. F. Fieser, THIS JOURNAL, **81**, 2276 (1959).

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(3) A. Butenandt and E. Hausmann, *Ber.*, **70**, 1154 (1937).

(4) L. F. Fieser, THIS JOURNAL, **75**, 4386 (1953).

(5) W. G. Dauben and G. J. Fonken, *ibid.*, **78**, 4736 (1956).

(6) C. Djerassi, D. Marshall and T. Nakano, *ibid.*, **80**, 4853 (1958).

(7) W. G. Dauben, G. A. Boswell, Jr., and G. H. Berezin, *ibid.*, **81**, 6082 (1959). I am greatly indebted to Professor Dauben for informing me of the recent work.