A sample of 2,3,5-trimethyl-L-arabonamide prepared according to Humphreys, Pryde and Waters[13] melted at 137.5–138° and had $[\alpha]^{23}D$ +16.9° (*c* 2.0 in water). A mixture of equal amounts of the D- and L-forms melted at 149–150°.

3,4,6-Trimethyl-N-methyl-D-glucosaminic Acid (VI).—2,3,5-trimethyl-D-arabinose (IV) (3.7 g.) was subjected to a cyanhydrin synthesis as described above for 2,5-dimethyl-D-arabinose. The final product of the reaction, 3,4,6-trimethyl-N-methyl-D-glucosaminic acid (VI) (1.39 g.) crystallized readily from absolute alcohol, m.p. 206–206.5°, $[\alpha]^{25}D$ +9.5° (initial) → +8.2° (final after 20 hours), (*c* 2.1 in water). Three recrystallizations of the acid did not alter its melting point and specific rotation.

Anal. Calcd. for $C_{10}H_{21}O_6N$: C, 47.79; H, 8.42; N, 5.57; OCH_3, 37.01. Found: C, 47.87; H, 8.35; N, 5.48; OCH_3, 37.5.

Acknowledgment.—The authors are indebted to Mr. J. F. Alicino and his associates for the microanalyses reported in this paper.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reductive Methylation of Steroid Ketones

BY JOHN C. BABCOCK[1] AND LOUIS F. FIESER

RECEIVED JULY 16, 1952

A dehydro derivative of methyl $\Delta^{9(11)}$-lithocholenate tentatively regarded by Fieser and Rajagopalan as a 3,9-oxide is actually the normal 3-ketone (I), and a product derived from it by hydrogenation in methanol–hydrobromic acid and characterized by the presence of an inert oxygen function is the 3β-methyl ether II. Comparable reductive methylations have been demonstrated with a saturated bile acid 3-ketone (VII), with coprostanone and with cholestanone.

On investigating the oxidation of methyl $\Delta^{9(11)}$-lithocholenate (V) and its oxide, Fieser and Rajagopalan[2] encountered two products that appeared to be of novel types. The product of oxidation of the 9,11-oxide was subsequently studied by Heymann and Fieser[3] and found to be a hemiketal with a 3,9-oxide bridge. That from the unsaturated hydroxy ester seemed abnormal because on hydrogenation in methanol containing hydrobromic acid it afforded a dihydro derivative that contained neither a hydroxyl nor a ketone function but appeared to contain an inert ether-oxygen atom. A 3,8-oxide formulation was tentatively considered,[2] although it failed to account for some of the observations.

At the time of the earlier work the Baird spectrophotometer available was incapable of distinguishing between a 3-ketone and an ester carbonyl group. The spectrum of Rajagopalan's original oxidation product, taken with improved apparatus at low speed and high resolution, has now revealed a distinct doublet in the carbonyl region with maxima at 5.79 and 5.83 μ (Chf). The inference that the substance is the normal oxidation product, methyl 3-keto-$\Delta^{9(11)}$-cholenate (I), was confirmed by formation of a semicarbazone and a 2,4-dinitrophenylhydrazone, and by formation of an identical product by Oppenauer oxidation of methyl $\Delta^{9(11)}$-lithocholenate, which excludes an allylic-type oxidation.

The product obtained by hydrogenation of I in methanol in the presence of hydrobromic acid, but not in absence of the acid, might still be a saturated, cyclic oxide. However, Dr. Rajagopalan's original samples as well as a fresh sample of the same properties all gave positive tests for unsaturation with tetranitromethane. The inference that the substance is in fact the unsaturated 3-methyl ether II was substantiated by the results of a methoxyl determination. The product obtained earlier[2] by further hydrogenation of II in acetic acid must then be the saturated 3-methyl ether III, and indeed an identical product was obtained by hydrogenation of methyl dehydrolithocholate (VII) in methanol–hydrobromic acid. The same ether also resulted from methanolysis of methyl lithocholate 3-tosylate (IV). Since in saturated systems tosylate displacement always proceeds with inversion, this result shows that the methoxyl group in II and III has the β-orientation.

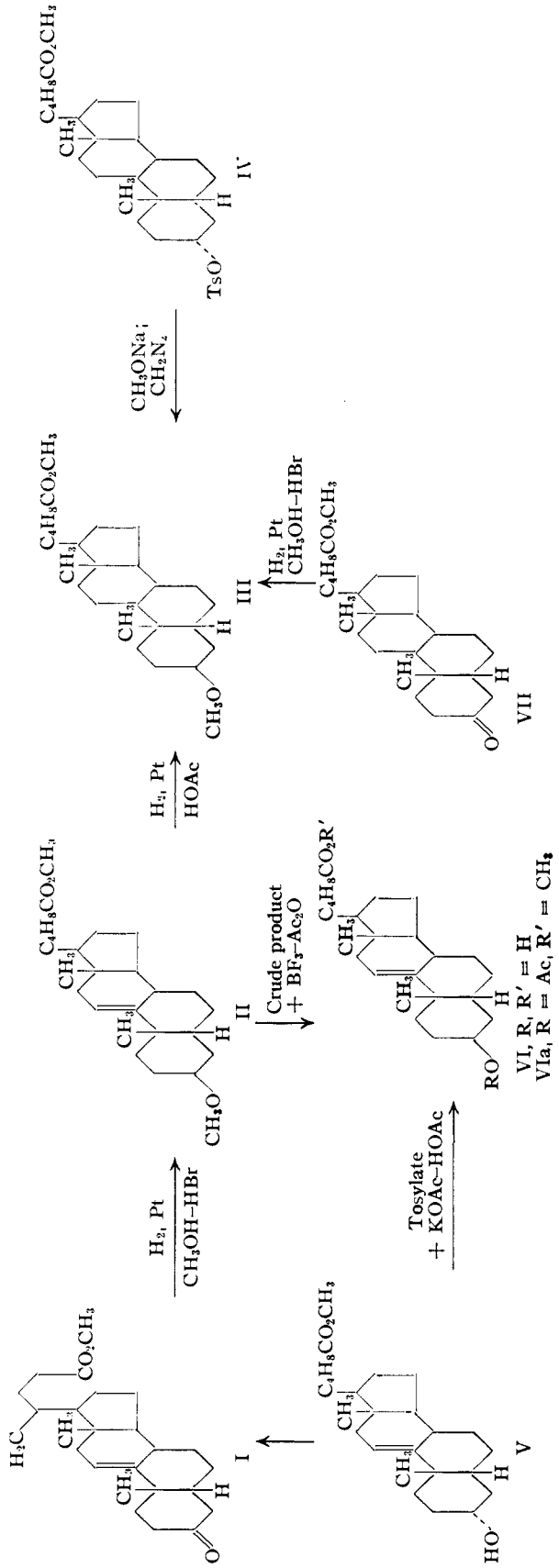
The true structures of the alcohols[2] resulting from lithium aluminum hydride reduction of II and III follow from the revised formulations of these compounds, as summarized in the Experimental part. A further product, isolated by Rajagopalan as the acetate in less than 1% yield by acetolysis of the unsaturated methyl ether II, was characterized as a hydroxycholenic acid, m.p. 210°, αD + 44° Di; methyl ester acetate, m.p. 183°, αD + 40° Di. It now seems likely that this acetate arose not from II but from a 3-hydroxy compound present as an impurity. The fact that the hydroxycholenic acid differs but little in rotation from its acetate methyl ester provided a clue to its identity. In the series of 3α-hydroxy bile acids the increment $\Delta^{\text{acetate ester}}$ = [M_D (3-acetate methyl ester) − M_D (3-hydroxy acid)] has a large positive value, +79 for lithocholic acid, +95 for $\Delta^{9(11)}$-lithocholenic acid,[4] + 100 for Δ^{11}-lithocholenic acid.[4] In contrast, the M_D increment for conversion of the hydroxy acid in question into its acetate ester is only +7, which means that the acid must belong to some other series. That this is the β-hydroxy series was suggested by the fact that the acetate methyl ester (αD + 40° Di) differs in rotation from methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate (α_D + 62.9 An[4]) to an extent closely comparable to the difference between methyl 3β-acetoxycholanate (αD + 23° Chf) and the epimeric 3α-acetoxy compound (αD + 45° Di). The structure thus suggested, methyl 3β-acetoxy-$\Delta^{9(11)}$-cholenate (VIa) for the acetate methyl ester, was established by preparation of an identical substance by solvolysis of the tosylate of methyl $\Delta^{9(11)}$-lithocholenate (V) with

(1) Du Pont predoctoral fellow, 1951–1952.

(2) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **73**, 118 (1951).

(3) H. Heymann and L. F. Fieser, *ibid.*, **73**, 5252 (1951).

(4) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).



potassium acetate in acetic anhydride. That the 9,11-double bond evidently escaped reduction under the conditions of formation of the 3β-hydroxy ester from I (and in attempted isomerization of VIa with palladium–charcoal[2]), is in keeping with other observations that such a bond is hydrogenable only with difficulty.[4]

The apparently novel formation of a methyl ether on hydrogenation of a ketone in methanol–hydrobromic acid is describable as a process of reductive methylation, comparable to the reductive alkylation of an amine through a Schiff base. The conversion of methyl dehydrolithocholate (VII) to the 3β-methoxy derivative (III) already cited is a second example that demonstrates lack of any dependence on a 9,11-double bond. Coprostanone on reductive methylation afforded in good yield a new methyl ether (configuration not established, probably β). Hydrogenation of cholestanone in methanol–hydrobromic acid gave the known cholestanyl methyl ether,[5,6] identical with a sample prepared by methanolysis of cholesteryl tosylate and hydrogenation.[6] The formation of the β-methoxy derivative in the acid-catalyzed reaction represents a steric course the opposite of that in the hydrogenation of cholestanone to epicholestanol in ether–hydrogen bromide.[7]

Experimental

Methyl 3-Keto-$\Delta^{9(11)}$-cholenate (I, Previously Called[2] "Methyl 3α,8α-Oxido-$\Delta^{9(11)}$-cholenate").—A simpler method of preparation consisted in adding a solution of 330 mg. of sodium dichromate dihydrate in 3 cc. of acetic acid dropwise over 1 hr. to a cooled solution of 1 g. of methyl $\Delta^{9(11)}$-lithocholenate in 10 cc. of acetic acid. After 8 hr. at 25° dilution with water caused separation of shiny flakes; 0.92 g., m.p. 109–110°. Repeated crystallization from dilute methanol or dilute acetone effected only slow purification, but a single crystallization from 60–90° ligroin gave 0.75 g. of I, m.p. and mixed m.p. with Rajagopalan's sample,[2] 117–119°; λ_{max}^{Chf} 5.79, 5.83 μ, $\lambda_{max}^{CS_2}$ 5.75, 5.82 μ.

Oxidation was also conducted by refluxing for 3 hr. a solution of 265 mg. of methyl $\Delta^{9(11)}$-lithocholenate in 8 cc. of benzene with 6 cc. of cyclohexanone and 585 mg. of aluminum isopropoxide. The mixture was diluted, acidified, steam distilled, and the product collected in ether and chromatographed. Benzene–petroleum ether mixtures eluted 99 mg. of I, m.p. 116.5–117.5° (no depression in m.p. when mixed with above sample), $\alpha^{22}D$ +35 ± 1° Chf.

The semicarbazone was obtained by refluxing 89 mg. of I in 10 cc. of methanol with 89 mg. of semicarbazide hydrochloride and 150 mg. of sodium acetate in 1 cc. of water for 3 hr., concentrating the solution to half volume and diluting with water. The crystallizate amounted to 127 mg., m.p. 189° dec. Recrystallization did not raise the m.p.; λ_{max}^{Cnl} 2.82, 3.0, 5.80, 5.92, 6.35 μ.

Anal. Calcd. for $C_{26}H_{41}O_3N_3$ (443.60): C, 70.39; H, 9.32. Found: C, 70.68; H, 9.32.

The 2,4-dinitrophenylhydrazone was prepared by warming 90 mg. each of I and 2,4-dinitrophenylhydrazine in 6 cc. of methanol for 1 min. The flocculent yellow precipitate was crystallized from chloroform–methanol, m.p. 203.5–206°, λ_{max}^{EtOH} 367.5 mμ (22,400).

Anal. Calcd. for $C_{31}H_{42}O_6N_4$ (566.68): C, 65.70; H, 7.47. Found: C, 65.71; H, 7.72.

Methyl 3β-Methoxy-$\Delta^{9(11)}$-cholenate (II, Formerly[2] "Methyl 3α,8α-Oxidocholanate").—As in the early work,[2] a mixture of 450 mg. of I and 45 mg. of platinum oxide in methanol merely absorbed hydrogen sufficient to saturate the catalyst until 5 drops of 48% hydrobromic acid were added, when 0.9 mole of gas was taken up rapidly. A first

(5) T. Wagner-Jauregg and L. Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

(6) J. L. Dunn, I. M. Heilbron, R. F. Phipers, K. M. Samant and F. S. Spring, *J. Chem. Soc.*, 1576 (1934).

(7) A. Windaus and Cl. Uibrig, *Ber.*, **47**, 2384 (1914).

crop of product on recrystallization from ether–methanol gave 0.29 g. of II, m.p. 113–115°; chromatography of the mother liquor material gave 35 mg. more of II and 25 mg. of methyl $\Delta^{9(11)}$-lithocholenate, m.p. 103–105°; in a separate experiment the latter ester was recovered unchanged after attempted hydrogenation under the above conditions.

The above sample of II gave a depression of 20° when mixed with I but showed no depression in m.p. when mixed with Rajagopalan's samples, all of which gave yellow colors with tetranitromethane in chloroform. The ester was recovered unchanged after treatment with sodium dichromate in acetic acid for 24 hr. at 25° and after attempted acetylation with pyridine–acetic anhydride. The following comparison shows that the original analyses[2] fit the revised formulation; the methoxyl determination (on Rajagopalan's sample) indicates the presence of two, not one, methoxyl groups.

Anal. Calcd. for $C_{26}H_{42}O_3$ (402.59): C, 77.56; H, 10.52; OCH_3, 15.41. Found: C, 77.52, 77.45; H, 9.98, 10.18[2]; OCH_3, 14.74.

Methyl 3β-Methoxycholanate (III ($C_{26}H_{44}O_2$), **Formerly "Methyl 8(?)-Hydroxycholanate").** (a) **From Methyl Dehydrolithocholate.**—A mixture of 256 mg. of methyl dehydrolithocholate, 0.25 cc. of methanol, 0.3 cc. of 48% hydrobromic acid and 24.9 mg. of platinum oxide absorbed almost one mole of hydrogen in ½ hr. After filtration from the catalyst the solution was concentrated to half volume and diluted with water, which gave an amorphous precipitate (125 mg.). Crystallization from methanol seemed unpromising, and hence the material was chromatographed. An early part, eluted by petroleum ether–benzene (9:1) was not identified: m.p. 85–87°, $\alpha^{22}D$ +22.5° Chf, saturated to $C(NO_2)_4$; found: C, 78.84; H, 10.94. An intermediate set of fractions afforded 100 mg. of methyl 3β-methoxycholanate, m.p. 103–104°, undepressed on admixture with Rajagopalan's sample obtained by hydrogenation of II in acetic acid. A third part, eluted by benzene and benzene–ether, seemed to consist of a mixture of 3-alcohols.

(b) **From Methyl Lithocholate 3-Tosylate.**—The tosylate was largely recovered unchanged after being refluxed for 2 hr. in methanol containing either a trace or an equivalent of sodium methoxide. Hence 0.7 g. of sodium was dissolved in 20 cc. of methanol, 200 mg. of tosylate was added, and the solution refluxed for 24 hr., diluted with 3 cc. of water, and refluxed 12 hr. longer. Acidification gave 90 mg. of **3β-methoxycholanic acid** ($C_{25}H_{42}O_2$, formerly[2] "8(?)-hydroxycholanic acid"), which formed micro plates from dilute acetone, m.p. 140–142°, $\alpha^{21.5}D$ +22.1 Di. Esterification with diazomethane afforded methyl 3β-methoxycholanate, m.p. and mixed m.p. with (a) 102–103°. The mother liquors of the free acid on esterification and chromatography afforded more ester, m.p. 103–104° (eluted by benzene–petroleum ether, 1:1).

Methyl Lithocholate 3-Tosylate (IV).—A solution of 500 mg. each of methyl lithocholate and tosyl chloride in 5 cc. of dioxide and 2.5 cc. of pyridine was let stand at 25° for 48 hr. and diluted with water. The initially oily product hardened on chilling to a solid; 0.61 g., m.p. 107–109°. Crystallization of a small sample from dilute acetone raised the m.p. to 110–112° (decomposing at 177° to a brown-black melt).

Anal. Calcd. for $C_{32}H_{48}O_5S$ (544.76): C, 70.55; H, 8.88; S, 5.88. Found: C, 70.17; H, 8.76; S, 6.35.

Methyl 3β-Acetoxycholanate.—A mixture of 200 mg. each of methyl lithocholate 3-tosylate and potassium acetate in 4 cc. of acetic acid containing several drops of acetic anhydride was refluxed for 75 min. and evaporated to dryness.[8] The crystalline residue was extracted with ether, washed and chromatographed. Benzene–petroleum ether (2:1) eluted 60 mg. of product, m.p. 164–165°, $\alpha^{22}D$ +21 ± 1° Chf.

(8) Essentially the method of Pl. A. Plattner and A. Fürst, *Helv. Chim. Acta*, **26**, 2266 (1943).

Anal. Calcd. for $C_{27}H_{44}O_4$ (432.62): C, 74.96; H, 10.25. Found: C, 74.98; H, 10.26.

The same saturated acetate ester was the chief product resulting (after acetylation) from attempted selective hydrogenation of the carbonyl group of methyl 3-keto-$\Delta^{9(11)}$-cholenate (100 mg., 13.4 mg. of platinum oxide, 10 cc. acetic acid; shaken with hydrogen for 40 min. at 25°). Chromatography afforded 60 mg. of fine plates, m.p. 169.5–171°, αD +24° Chf. The sample gave a faint color with tetranitromethane, but yielded no oxide and did not depress the m.p. of the sample prepared from the tosylate.

Methyl $\Delta^{9(11)}$-lithocholenate 3-tosylate was prepared by the method described for the saturated tosylate. Two crystallizations from dilute acetone gave material, m.p. 111–112° (clear, decomposing to a black melt at 170°).

Anal. Calcd. for $C_{32}H_{46}O_5S$ (542.75): C, 70.81; H, 8.54. Found: C, 71.41; H, 8.47.

Methyl 3β-Acetoxy-$\Delta^{9(11)}$-cholenate (VIa, Formerly[2] "Methyl ?-Lithocholenate Acetate").—A mixture of 440 mg. each of the above tosylate and potassium acetate in 8 cc. of acetic acid containing several drops of acetic anhydride was refluxed for 90 min., evaporated to dryness, and the residue extracted with ether. The washed and dried extract was evaporated to a small volume and the solvent largely displaced with ligroin; 130 mg. of shiny plates separated. One recrystallization from ether–ligroin gave 100 mg. of acetate ester, m.p. 178–180°, $\alpha^{22}D$ +38 ± 2° Di.

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.30; H, 9.82. Found: C, 75.33; H, 10.01.

This material showed no depression in m.p. when mixed with Rajagopalan's sample. Saponification gave **3β-hydroxy-$\Delta^{9(11)}$-cholenic acid** (formerly "?-lithocholenic acid") as long needles from dilute acetone, m.p. 174–175°, αD +42° Chf.

Other Revisions.—The substance previously described[2] as "8(?)-hydroxycholanyl alcohol-B" is **3β-methoxy-$\Delta^{9(11)}$-cholenyl alcohol** ($C_{25}H_{42}O_2$), m.p. 146–147°, $\alpha^{22}D$ +39° Di (we found the substance to be unsaturated to tetranitromethane). That described as "8(?)-hydroxycholanyl alcohol-A" is **3β-methoxycholanyl alcohol** ($C_{25}H_{44}O_2$), m.p. 114–116°, $\alpha^{22}D$ +25° Di, saturated to $C(NO_2)_4$.

Coprostanyl Methyl Ether.—A mixture of 400 mg. of coprostanone, m.p. 62–63°, and 39 mg. of platinum oxide in 40 cc. of methanol and 0.4 cc. of 48% hydrobromic acid absorbed 0.9 mole of hydrogen, when the catalyst coagulated. On chromatography, petroleum ether eluted 100 mg. of ether melting, after one crystallization from ethyl acetate–methanol, at 62–63°, $\alpha^{23.5}D$ +27.5 ± 1° Chf. A mixture of the product with starting material was depressed 5°.

Anal. Calcd. for $C_{28}H_{50}O$ (402.68): C, 83.51; H, 12.52; OCH_3, 7.71. Found: C, 83.05; H, 12.63; OCH_3, 7.88.

Oxidation of the tail fractions from the chromatograph afforded 55 mg. of crude coprostanone, m.p. 55–59°.

Cholestanyl Methyl Ether.—A suspension of 150 mg. of cholestanone and 16 mg. of platinum oxide in 25 cc. of methanol and 0.25 cc. of 48% hydrobromic acid absorbed 1 mole of hydrogen in 4 hr. Dilution of the filtered solution gave 110 mg. of shiny plates, m.p. 76–80° (unclear). A solution of the product in petroleum ether containing a little benzene was filtered through a column of alumina to remove hydroxylic impurities; the ether then melted at 81–82°, $\alpha^{23}D$ +21.9 ± 1° Chf.[5]

For preparation of a comparison sample, 1 g. of cholesteryl tosylate was refluxed with 25 cc. of methanol for 1.75 hr., after which 0.5 g. of cholesteryl methyl ether crystallized, m.p. 82–83° (a mixture with cholestanyl methyl ether was depressed 1°). Hydrogenation in acetic acid (platinum oxide) and one crystallization from methanol gave cholestanyl methyl ether, m.p. 81–82°, $\alpha^{21.5}D$ +20.6 ± 1° Chf. The samples prepared by the two methods showed no depression in m.p. on admixture and had identical infrared spectra.

CAMBRIDGE, MASSACHUSETTS