tion), pH adjusted to 10.0 with 10% sodium hydroxide, was added slowly during 2.5 hours. Distillation of the colorless product yielded a forerun of nitromethane and water and 58.6 g. (64% based on formaldehyde), of β-nitroethanol, b.p. 95–99° at 7–8 mm.

Condensation of Methyl Ethyl Ketone with Formaldehyde in Modified Apparatus.—The apparatus used is shown in Fig. 5. In the boiling flask was placed 504 g. (7.0 moles) of methyl ethyl ketone and 2 g. of citric acid. During a period of seven hours, 320 g. (4.0 moles) of Merck 37.5% formaldehyde (adjusted to pH 10.5 with sodium hydroxide) was added dropwise, while the column was operated at the point of incipient flooding. Distillation of the products through a short Claisen-type still-head gave 270 g. (66.1%) of 4-hydroxy-3-methyl-2-butanone, b.p. 90–92° at 20 mm.

The previous experiment was duplicated exactly except that the trap between the condenser and the column was removed. Distillation of the products gave 341.4 g. (83.6%) of 4-hydroxy-3-methyl-2-butanone, b.p. 90–92° at 20 mm.

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[Contribution from the Research Laboratories of Merck & Co., Inc.]

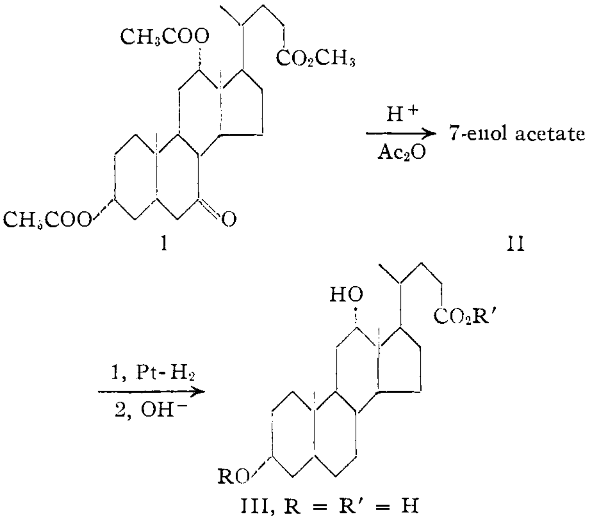
A New Route to Desoxycholic Acid

By Ralph Hirschmann, Malcolm Brown and N. L. Wendler

Catalytic hydrogenation of the enol acetates of 7-keto bile acids has provided a new route to the corresponding 7-desoxy acids.

At the time this work was initiated, the only method available for the synthetic preparation of desoxycholic acid consisted in the oxidation of cholic acid or its ester to 3(α),12(α)-dihydroxy-7-ketocholanic acid followed by a Wolff–Kishner reduction of this intermediate.[1] We wish to report a new method for effecting the conversion of cholic to desoxycholic acid.

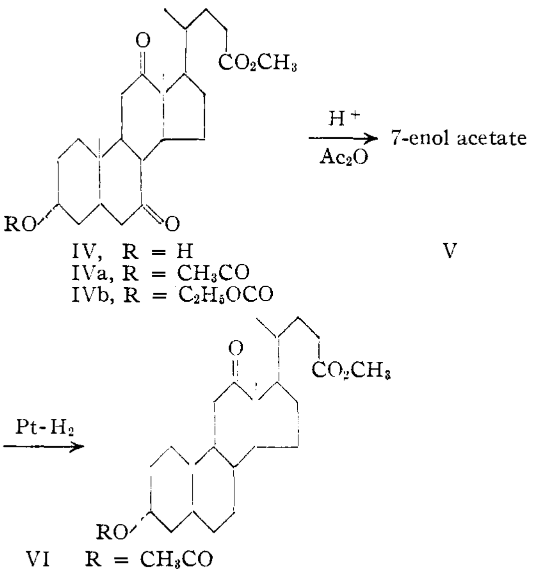
Treatment of methyl 3(α),12(α)-diacetoxy-7-ketocholanate (I) under conditions of enol acetylation either with acetic anhydride[2] or isopropenyl acetate[3] in the presence of p-toluenesulfonic acid was found to produce methyl 3(α),7,12(α)-triacetoxycholenate (II). Subsequent hydrogenation of this individual with platinum in acetic acid followed by saponification afforded desoxycholic acid (III) in 30–35% yield from I.



I II

III, R = R' = H
IIIa, R = CH₃CO–, R' = CH₃

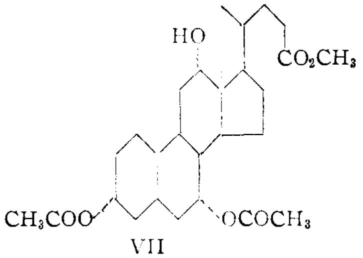
Under similar conditions methyl 3(α)-acetoxy-7,12-diketocholanate (IVa) yielded the 7-*mono*-enol acetate V. This compound was in turn hydrogenated to give methyl 3(α)-acetoxy-12-ketocholanate (VI) and its 12-dihydro derivative IIIa as the predominant products together with small amounts of cholic acid ester diacetate (VII).[4]



IV, R = H
IVa, R = CH₃CO
IVb, R = C₂H₅OCO

V

VI R = CH₃CO
VIa R = C₆H₅CO



VII

It is noteworthy that the 12-carbonyl group of IV did not participate to any measurable extent in the enol acetylation reaction. This fact was further substantiated by the failure of VIa to react under conditions of enol acetylation.

Experimental

Methyl 3(α),7-Diacetoxy-12-keto-cholenate (Va).—A mixture of acetic acid and acetic anhydride was distilled[2] for

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[1] Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N.Y., 1949, p. 128.

[2] Bedoukian, This Journal, **67**, 1430 (1945).

[3] Hagemeyer and Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

[4] It has been observed recently by Inhoffen, Stoeck, Kölling and Stoeck (*Ann.*, **568**, 52 (1950)) that cholestenone can be converted along similar lines to cholestane.

six hours from a solution of 50 g. (0.120 mole) of IV (m.p. 153–155.5°)[5] and 22.8 g. (0.120 mole) of *p*-toluenesulfonic acid monohydrate in 1 l. of acetic anhydride in a nitrogen atmosphere. The residual solution was concentrated *in vacuo* to a dark brown sirup which was taken up in 600 cc. of ether and washed successively with water, 1 *N* sodium bicarbonate solution and again with water. After drying over sodium sulfate and removal of the ether *in vacuo* a dark gummy oil was obtained which was digested portionwise with a total of 2.5 l. of petroleum ether (b.p. 90–100°) until only 0.6 g. of insoluble tars remained. The solution was passed through 400 g. of acid washed alumina and eluted with a total of 4.5 l. of benzene–petroleum ether (b.p. 90–100°) mixtures. From the eluates 26.4 g. (44% yield) of the desired monoenol acetate (V), m.p. 118–121°, was obtained. A sample was purified by repeated recrystallization from petroleum ether (b.p. 68–69°) to afford slender prisms, m.p. 121.5–123°.

Anal. Calcd. for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 69.41; H, 8.39.

The mother liquors from further benzene–petroleum ether eluates afforded 20.3 g. of an oil and methanol eluted 4.8 g. of crystalline material, m.p. 161–162°. A mixed m.p. of the latter with an authentic specimen of IVa was 161–163°.

A 0.5-g. aliquot from the above 20.3 g. of oily fraction was dissolved in 15 cc. of 1 *N* methanolic hydrogen chloride and allowed to stand at room temperature overnight. After removal of the solvent *in vacuo* and recrystallization from ethyl acetate, 0.15 g. of IV, m.p. 156.8–158.0°, could be isolated. A mixed m.p. with an authentic sample showed no depression. In a similar experiment employing 0.5 g. of crystalline enol acetate, m.p. 120–122°, there was obtained 0.35 g. (84% yield) of IV, m.p. 155.4–156.8°.

Treatment of IVb[6] with acetic anhydride and *p*-toluenesulfonic acid afforded **methyl 3(α)-carbethoxy-7-acetoxy-12-ketocholenate** (Vb), m.p. 111.5–113°.

Anal. Calcd. for $C_{30}H_{44}O_8$: C, 67.65; H, 8.33. Found: C, 67.48; H, 8.24.

The enol acetate V could also be prepared by the method of Hagemeyer[3] employing isopropenyl acetate as the enol-acetylating agent.

Methyl 3(α)-Acetoxy-12-ketocholanate (VI).—A 0.874-g. sample (0.00174 mole) of the enol acetate (Va) (m.p. 121–122°) was dissolved in 50 cc. of glacial acetic acid and hydrogenated in the presence of 0.3 g. of platinum oxide at room temperature and atmospheric pressure. After 45 minutes the hydrogen uptake had ceased. The catalyst was removed by filtration and hydrogenation was resumed with 0.3 g. of fresh platinum oxide. The reaction was essentially completed after two hours although the hydrogenation was allowed to continue overnight. Removal of the solvent from the filtered solution afforded a viscous oil. This oil was taken up in 4 cc. of glacial acetic acid and treated over a period of 30 minutes with four 0.4-cc. portions of an oxidizing solution prepared from 4.1 g. of chromic anhydride, 4 cc. of water and 34 cc. of glacial acetic acid. The reaction mixture was swirled repeatedly and allowed to stand at room temperature for an additional hour and 30 minutes. The excess oxidizing agent was decomposed with methanol and the solvents were removed at reduced pressure on the steam-bath. The residue was slurried with a mixture of ether and 2 *N* sulfuric acid. The organic layer was separated and washed with sulfuric acid until colorless, twice with water, with a 5% solution of sodium bicarbonate, with water and finally with a saturated solution of sodium chloride. Removal of the solvent afforded a colorless crystalline solid which was recrystallized from ethanol–water to give 0.370 g. (48% yield) of material, m.p. 146–150°; the m.p. was not depressed on admixture with a sample of authentic VI. A single recrystallization raised the m.p. to 150–152°. The infrared absorption spectrum of this material was found to be identical with that of VI. The pure compound is reported[7] to melt at 150–151°.

Further processing of the mother liquors from the initial recrystallization afforded a second crop of crystalline material (0.255 g., m.p. 151–154°) and a third crop (0.038 g., m.p. 141–148°). Recrystallization of the second crop from ethanol–water raised the m.p. to 154–167° (0.215 g.). Therefore, this material was combined with the third crop, dissolved in a mixture of benzene–petroleum ether (b.p. 68–69°) and passed through 20 g. of acid washed alumina. The major fraction isolated (0.235 g.) proved to be a mixture but after retreatment with diazomethane it was possible to isolate 0.140 g. of methyl 3α,7α-diacetoxy-12-ketocholanate, m.p. 177–179°, which was characterized by mixed m.p. determination and comparison of the infrared spectrum with authentic material. The pure compound is reported to melt at 177–179°.[6,8]

In one run (5.0-g. scale) hydrogenation was stopped after two moles of hydrogen had been absorbed. After removal of the solvent from the filtered solution the residual gum was dissolved in ether and washed with water, an aqueous solution of sodium bicarbonate, and again with water. Removal of the ether gave a colorless gum from which 0.5 g. of VI, m.p. 150–152°, could be obtained after repeated recrystallization from alcohol. Chromatographic purification gave an additional 0.2 g. of VI, m.p. 149–151°. From the eluates 0.38 g. of **methyl 3(α),7(α)-diacetoxy-12(α)-hydroxycholanate (VII)**, m.p. 185.5–187°, could be isolated. The m.p. was not depressed on admixture with an authentic sample of VII. The pure compound is reported to melt at 187–188°.[6,9]

Anal. Calcd. for $C_{29}H_{46}O_7$: C, 68.74; H, 9.35. Found: C, 68.61; H, 9.43.

3(α),12(α)-Dihydroxycholanic Acid (Desoxycholic Acid) (III).—The enol acetate II was prepared essentially as described above for V. In this manner 5.4 g. (0.01 mole) of I, m.p. 115–117°, afforded after chromatographic purification of the crude reaction product 4.3 g. of an oil from the petroleum ether eluates. The oily enol acetate, after dissolving in acetic acid, was reduced over Adams catalyst as described above for the 12-keto series. The semicrystalline product isolated from the reduction step was saponified. Acidification with dilute hydrochloric acid afforded an amorphous solid from which 0.911 g. of VIa, m.p. 173–173.5°, could be isolated by crystallization from acetone. Concentration of the mother liquors yielded 0.680 g. of amorphous material which gave 0.325 g. of crystalline acid, m.p. 172–172.5°, bringing the over-all yield of desoxycholic acid from I to 32%. Working up the mother liquors afforded additional amounts of crystalline material melting over a wider range. The desoxycholic acid isolated as described above was identified by mixed m.p. determination with authentic material and by comparison of the infrared spectra. The sample did not give a color reaction with tetranitromethane and the m.p. of the acid was depressed on admixture with apocholic acid. Our acid was further characterized by conversion into **methyl 3(α),12(α)-diacetoxycholanate**, m.p. 117–117.5°, with diazomethane followed by acetylation with pyridine and acetic anhydride on a steam-bath for three hours. A mixed m.p. with an authentic sample of the ester showed no depression. The *infrared* spectra of the two specimen were identical in every detail.

Attempted Enolacetylation of VIa.—A mixture of VIa (1 mole), *p*-toluenesulfonic acid (0.1 mole) and an excess of isopropenyl acetate was maintained at gentle reflux for five hours.[3] The reaction mixture was worked up without recourse to chromatography. Only starting material could be obtained. In another experiment 6.1 g. of VIa was submitted to enolacetylating conditions (acetic anhydride and *p*-toluenesulfonic acid[2]). The reaction mixture afforded 5.5 g. of a dark viscous oil which was purified by chromatography. Petroleum ether eluted first 0.88 g. of a viscous oil which did not crystallize but which is considered to be essentially unchanged starting material on the basis of the infrared absorption spectrum. Further petroleum ether eluates afforded 2.7 g. of crystalline fractions from which the starting ketoester was readily obtained by recrystallization from petroleum ether.

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(5) Borsche and Hallwass, *Ber.*, **55**, 3318 (1922).

(6) Fieser and Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

(7) Gallagher and Long, *J. Biol. Chem.*, **162**, 495 (1946).

(8) (a) Wieland and Kapitel, *Z. physiol. Chem.*, **212**, 269 (1932); (b) Plattner and Heusser, *Helv. Chim. Acta*, **27**, 748 (1944).

(9) Lardon and Reichstein, *ibid.*, **30**, 1542 (1947).