cipitate formed which was collected and crystallized from absolute ethanol, m. p. 211° (dec.).

Anal. Calcd. for $C_{17}H_{19}N_3O_3 \cdot H_2SO_4$: C, 51.36; H, 5.33; N, 7.06. Found: C, 51.30; H, 5.19; N (Dumas), 6.99.

4-Quinolyl-4'-tetrahydropyranylmethyl Ketone.—Twenty-eight grams of the crude imidonitrile was allowed to stand for two days with 100 cc. of concd. sulfuric acid. The solution was then diluted with 100 cc. of water and the whole was refluxed five hours. The mixture was cooled, diluted and basified with sodium carbonate. The precipitated oil was taken into ether, dried over potassium carbonate and acidified with 48% hydrobromic acid. The hydrobromide crystallized from absolute ethanol as yellow plates melting at 214° (dec.).

Anal. Calcd. for $C_{16}H_{18}NO_2 \cdot HBr$: C, 56.97; H, 5.68. Found: C, 56.75; H, 5.73.

In our hands the bromination of both 4-phenacetyl quinoline and the corresponding tetrahydropyranyl ketone proved quite unsatisfactory. A number of products were isolated but their identity was dubious and they proved valueless for synthetic purposes.

Acknowledgment.—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel W. Blackman for the micro-analyses here recorded.

Summary

1. The condensations of 4-cyanoquinoline with benzyl cyanide and tetrahydropyrane-4-acetonitrile using halomagnesium dialkylamides as condensing agents have been studied. While feasible, these condensations appear inferior to the more usual ester condensations, a marked complication being amidine formation between the condensing agent and the aromatic nitrile.

2. The additions of halomagnesium dialkyl or alkyl aryl amides to aromatic nitriles proceed readily and with good yields, thus constituting a useful synthesis of N,N-disubstituted amidines. A particular advantage of the reaction is its relative independence of steric hindrance.

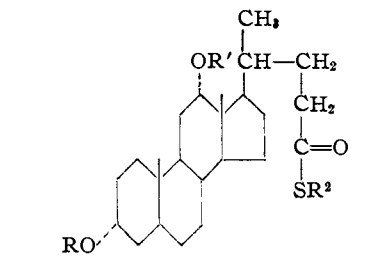
TUCKAHOE 7, NEW YORK RECEIVED AUGUST 27, 1947

[CONTRIBUTION FROM THE RESEARCH DIVISION, THE UPJOHN COMPANY]

Steroid Acids and Their Transformation Products. II. Desulfurization of Thiol Esters of Desoxycholic Acid[1a]

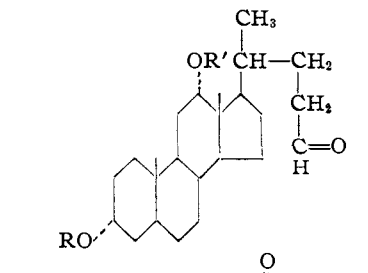
BY GEORGE B. SPERO, A. VERN MCINTOSH, JR., AND ROBERT H. LEVIN

The preparation of a number of thiol esters of steroid acids, including ethyl 3(α),12(α)-diformoxythiolcholanate (Ia),[1b] was reported recently.[2] According to the literature desulfurization of thiol esters with Raney nickel catalyst may yield alcohols[3] or aldehydes.[4] In our laboratory the course of the desulfurization of I was found to be dependent on the character of the Raney nickel catalyst. Using freshly prepared standard Raney nickel[5] the ethyl thiol ester (Ia) was converted to the cholane alcohol (III) and traces of the cholanic aldehyde (II). These results were obtained with 60 to 90% alcohol as a solvent, reflux times of one to five hours, and a ratio of 5 to 20 g. of catalyst per gram of thiol ester. When the more active W-4 Raney catalyst[6] was used, the thiol ester (Ia) was rapidly and quantitatively reduced and desulfurized to the alcohol (III). Karabinos[7] has suggested that if the reaction is interrupted immediately after the thiol ester has disappeared (as tested by odor after acidification) a good yield of



Ia, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = C_2H_5$

b, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = CH_2C_6H_5$



IIa, R = R' = $\overset{O}{\overset{\|}{C}}$H

b, R = H; R' = $\overset{O}{\overset{\|}{C}}$H

c, R = R' = H

(1a) Presented before the Division of Medicinal Chemistry at the 112th A. C. S. Meeting, New York, September, 1947.

(1b) Formulation of desoxycholic acid as 3(α),12(α) is according to the latest stereochemical evidence. For a discussion see the review article by Reichstein and Reich, *Ann. Rev. Biochem.*, **15**, 162 (1946).

(2) Levin, McIntosh, Spero, Rayman and Meinzer, THIS JOURNAL, **70**, 511 (1948).

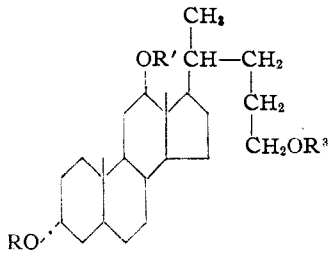
(3) (a) Prelog, Norymberski and Jeger, *Helv. Chim. Acta*, **29**, 360 (1946); (b) Jeger, Norymberski, Szpilfogel and Prelog, *ibid.*, **29**, 684 (1946); (c) Ruzicka, Szilfogel and Jeger, *ibid.*, **29**, 1520 (1946).

(4) Wolfrom and Karabinos, THIS JOURNAL, **68**, 1455 (1946).

(5) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 20.

(6) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(7) Private communication.



IIIa, R = R³ = H; R′ = C(=O)—H
b, R = R′ = R³ = H
c, R = R′ = R³ = C(=O)—CH₃

aldehyde may be obtained. This method was not practical for us, apparently because even our standard Raney Nickel[5] was more active than the catalyst used by Wolfrom and Karabinos,[4,8] and also because of the small quantities of high molecular weight esters with which we were working.

However, we have been able to produce the cholanic aldehyde (II) in good yields by partially deactivating the standard Raney nickel. Two deactivation procedures were tried. Heating the catalyst with an inert solvent while passing a stream of nitrogen through for twenty-four hours did not give sufficient deactivation. Refluxing with acetone for two hours under standardized conditions was found to give reproducible results, and the aldehyde could then be obtained by adding the thiol ester in acetone–water and refluxing for an additional hour. The aldehyde (II) from ethyl 3(α),12(α)-diformoxythiolcholanate (Ia) was isolated in 60–80% yields as the crude semicarbazone, apparently a mixture of the mono- and diformoxy compounds. Separation of the pure diformyl compound as the semicarbazone by recrystallization could only be accomplished in low yield. The 2,4-dinitrophenylhydrazone of the crude aldehyde (II) was also prepared. The hydrochloric acid used in the dinitrophenylhydrazone preparation apparently caused the hydrolysis of both formyl groups. Benzyl 3(α),12(α)-diformoxythiolcholanate, (Ib) prepared by the previously described methods[2] but not crystallized, was similarly desulfurized to give the C-24 aldehyde. The free aldehyde was isolated from the crude reaction mixture via its bisulfite addition complex according to the procedure developed in this laboratory for the 3-substituted bisnor-Δ^5-cholenic aldehyde.[9] Hydrolysis of the formyl groups occurred during the process. Crystallization from dilute acetic acid and chloroform–hexane gave 3(α),12(α)-dihydroxycholan-24-al (IIc). The experimental data indicate that the desulfurization to produce the aldehyde takes place to the extent of 60–80%, but that the choice of a diformyl derivative has made the isolation of pure products difficult in this instance.

As previously noted,[2] the formoxy groups at positions 3 and 12 are not firmly bound. During the refluxing of ethyl 3(α),12(α)-diformoxythiolcholanate with W-4 Raney nickel in 80% ethanol there was complete deformylation at position 3 and partial deformylation at position 12, giving a mixture of 3(α),24-dihydroxy-12(α)-formoxycholane (IIIa), m. p. 185–186.5°, and 3(α),12(α),24-cholanetriol (IIIb), m. p. 90–125°, which could be separated by fractional crystallization. A better method of separation was chromatography over alumina which gave 60% of the triol monoformate (IIIa), and 40% of the triol (IIIb). When the monoformate (IIIa) was rechromatographed it was recovered unchanged, further indicating that deformylation at position 12 was not due to the alumina. Saponification of IIIa gave the triol (IIIb); however, the compound was difficult to purify to constant m. p. because it formed various hydrates. Acetylation with acetic anhydride and pyridine gave 3(α),12(α),24-triacetoxycholane (IIIc), which crystallized beautifully and gave good analyses. Saponification of the triacetate (IIIc) again gave a triol of unsharp m. p. and variously hydrated.

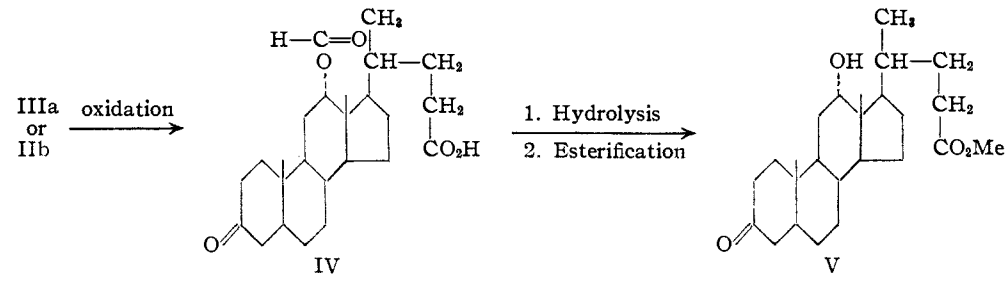
The structure of the monoformoxy triol (IIIa) was postulated as 3(α)-hydroxy,12(α)-formoxy because of the well-known greater ease of hydrolysis of 3-esters as compared to 12-esters in desoxycholic acid. To prove the correctness of this structure, the monoformate (IIIa) was oxidized with chromic acid in acetic acid at room temperature. The resulting 3-keto acid (IV) was not crystallized, but on hydrolysis followed by esterification gave a good yield of the known methyl 3-keto-12-(α)-hydroxycholanate (V).[10]

This series of reactions was repeated on the crude aldehyde (II) to give a 55% yield of methyl 3-keto-12(α)-hydroxycholanate (V). There remained the possibility that our conditions of oxidation might have caused deformylation and then a partial oxidation of the 3,12-dihydroxy compound to the 3-keto-12-hydroxycholanic acid. Accordingly, using the same experimental conditions, the cholantriol (IIIb) was oxidized to dehydrodesoxycholic acid and methyl diformyldesoxycholate (VI) was recovered substantially unchanged. Methyl diformyldesoxycholate, which apparently has not been recorded previously in the literature, was prepared by direct formylation of methyl desoxycholate. The diformyl compound (VI) was selectively deformylated in the 3-position using the chromatographic technique previously developed,[2] and the resulting 3-hydroxy com-

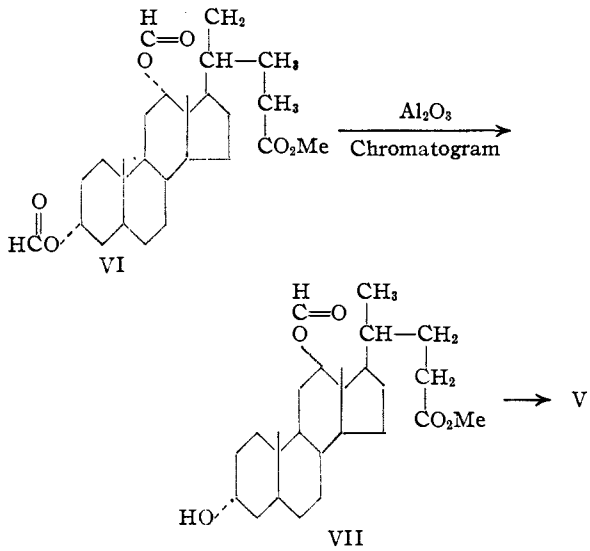
(8) In a check experiment we reduced ethyl thiol benzoate with standard Raney nickel catalyst following the directions of Wolfrom and Karabinos[4] and obtained just a trace of benzaldehyde. It is possible that the aldehyde is not even an intermediate in the formation of the alcohol from the thiol ester. Thus, in desulfurization experiments with ethyl 3(α),12(α)-diacetoxy-*nor*-thiolcholanate (to be reported shortly) we were able to obtain a good yield of alcohol, recovery of most of the remaining material as thiol ester, and just a trace of aldehyde, isolated as the semicarbazone.

(9) Centolella, Heyl and Herr, to be published shortly

(10) Yamasaki and Kyogoku, *Z. physiol. Chem.*, **233**, 29 (1935).



pound (VII) was converted to methyl 3-keto-12-(α)-hydroxycholanate (V).



Experimental[11,12]

Desulfurization of Ethyl 3(α),12(α)-Diformoxythiolcholanate (Ia) with Deactivated Raney Nickel. Aldehyde Formation.—Standard Raney nickel[5] (20 g.) was added to 60 ml. of acetone and heated under reflux with mechanical stirring for two hours. A solution of 2 g. (0.004 mole) of the thiol ester (Ia) in 40 ml. of acetone and 40 ml. of water was then added and refluxing was continued for an additional hour. The catalyst was separated by filtration and the filtrate concentrated *in vacuo* to a volume of 50 ml., then extracted with 100 ml. of ether. The ether was washed in portions with 100 ml. of cold 1% sodium hydroxide, 100 ml. of 1 *N* hydrochloric acid and 300 ml. of water. After drying over anhydrous sodium sulfate and evaporating to dryness *in vacuo*, 1.8 g. of crude aldehyde was obtained as a colorless oil.

Anal. Calcd. for the diformoxy aldehyde (IIa) $C_{26}H_{40}O_6$: C, 72.19; H, 9.32. Calcd. for the monoformoxy aldehyde (IIb) $C_{24}H_{40}O_4$: C, 74.21; H, 9.97. Calcd. for the dihydroxy aldehyde (IIc) $C_{24}H_{40}O_3$: C, 76.54; H, 10.71. Found: C, 72.94, 73.06; H, 9.39, 9.59.

The **semicarbazone** was prepared from the crude aldehyde from the desulfurization of 2 g. of thiol ester. This was dissolved in 80 ml. of 3A alcohol[13] and a solution of 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate in 20 ml. of water was added. The resulting solution was heated under reflux for two hours, cooled, and the product precipitated by the addition of 200 ml. of water; yield 1.8 g., m. p. 170–185°. Several crystallizations from methanol gave a product melting at 217–220°.

Anal. Calcd. for the diformoxy semicarbazone $C_{27}H_{43}O_5N_3$: C, 66.23; H, 8.85; N, 8.58. Calcd. for monoformoxy semicarbazone $C_{26}H_{43}O_4N_3$: C, 67.64; H, 9.39, N, 9.10. Calcd. for diol semicarbazone $C_{25}H_{43}O_3N_3$: C, 69.24; H, 10.00; N, 9.68. Found: C, 66.44, 66.39; H, 8.49, 8.48; N, 8.36, 8.30.

The **2,4-dinitrophenylhydrazone** was prepared by dissolving 860 mg. of the crude aldehyde in 70 ml. of 3A alcohol and adding 560 mg. of 2,4-dinitrophenylhydrazine. The solution was heated to boiling and 1 ml. of hydrochloric acid added. After refluxing for twenty-five minutes the solution was concentrated to half volume and allowed to cool, giving 520 mg. of product, m. p. 105–140°. An additional 120 mg. of product was obtained by concentrating the mother liquor. These fractions were combined and recrystallized from methanol to give pure 2,4-dinitrophenylhydrazone, m. p. 157–158°.

Anal. Calcd. for the diformoxy derivative $C_{32}H_{44}O_8N_4$: C, 62.72; H, 7.24; N, 9.15. Calcd. for the monoformoxy derivative $C_{31}H_{44}O_7N_4$: C, 63.68; H, 7.59; N, 9.58. Calcd. for the dihydroxy derivative $C_{30}H_{44}O_6N_4$: C, 64.72; H, 7.97; N, 10.06. Found: C, 64.32, 64.48; H, 8.22, 8.23; N, 10.22, 10.29.

3(α),12(α)-dihydroxycholan-24-al (IIc) was obtained by treating the crude reaction product from the desulfurization of 3 g. of ethyl thiol ester (Ia) with sodium bisulfite and subsequent decomposition of the aldehyde bisulfite complex with sodium carbonate.[9] The yield of aldehyde material was 1.12 g. (49%). Saponification of the formyl groups occurs during this decomposition. The aldehyde was crystallized from 50 ml. of dilute acetic acid and then repeatedly from chloroform–hexane, giving 0.27 g. (12%), m. p. 155.5–156.6°.

Anal. Calcd. for $C_{24}H_{40}O_3 \cdot H_2O$: C, 73.05; H, 10.73. Found: C, 73.38; H, 10.22.

Benzyl 3(α),12(α)-diformoxythiolcholenate (1b), prepared from 4.5 g. (0.01 mole) of 3,12-diformoxydesoxycholic acid and 2.4 g. of lead benzyl mercaptide, but not crystallized, was similarly desulfurized using 40 g. of deactivated nickel in 160 ml. of acetone and 80 ml. of water to yield 3.72 g. of aldehyde fraction. Portions of this crude aldehyde were converted to the identical semicarbazone and 2,4-dinitrophenylhydrazone derivatives described above.

Treatment of Ethyl 3(α),12(α)-diformoxythiolcholanate (Ia) with W-4 Raney Nickel. Alcohol formation.—To 2.0 g. (0.004 mole) of the thiol ester (Ia) in 40 ml. of 3A alcohol was added 10 g. of W-4 Raney nickel catalyst[6] and 10 ml. of water. The mixture was heated under reflux for one hour and the catalyst was separated by filtration and washed with 20 ml. of 3A alcohol. The filtrate was diluted with 200 ml. of water and extracted with 3 100 ml. portions of ether. The ether phase was washed with 100 ml. of 0.15 *N* sodium hydroxide, 300 ml. of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue, which weighed 1.7 g., was dissolved in warm alcohol and water added to incipient cloudiness. On cooling, 0.7 g. of oil settled out and was separated by decantation. The mother liquor was diluted with water and cooled, giving 0.47 g. of crystalline material, m. p. 143–160°. Three crystallizations from alcohol–water

(11) All analyses and rotations by the Upjohn microanalytical group.

(12) All m. p.'s are corrected unless otherwise indicated.

(13) 3A alcohol is commercial 95% alcohol denatured by the addition of 5% methanol.

gave pure 3(α),24-dihydroxy-12(α)-formoxycholane (IIIa), m. p. 185–186.5°; $[\alpha]^{25}D$ + 86.6° (100.5 mg. in 10 cc. chloroform; 1 dcm. tube; α, +0.87°).

Anal. Calcd. for $C_{25}H_{42}O_4$: C, 73.84; H, 10.41. Found: C, 73.91; H, 10.46.

Further dilution of the mother liquor, after separation of (IIIa), yielded 0.37 g. of 3(α),12(α),24-trihydroxycholane (IIIb), m. p. 90–110°. We were unsuccessful in purifying this compound to a sharp m. p. because of its tendency to solvate. It crystallized nicely from acetone–benzene, m. p. 105–125°, and from alcohol–water, m. p. 106–118°. However, it formed a beautiful triacetoxy compound, m. p. 79.5–80.5°, which will be described below.

Although IIIa and IIIb could be separated by fractional crystallization, chromatography over alumina[14] proved to be a much better method. A portion of the crude reaction product (850 mg.) was dissolved in 150 ml. of benzene and the solution was run through 39 g. of alumina contained in a column 2 cm. in diameter. The column was eluted with three 33-ml. portions each of benzene, benzene and 0.4% methanol, benzene and 1% methanol, benzene and 2% methanol, benzene and 4% methanol, and benzene and 8% methanol. Two separate fractions were obtained. In the benzene and 4% methanol there was 538 mg. of compound IIIa, m. p. 182–186°, and in the benzene and 8% methanol there was 232 mg. of the triol (IIIb), m. p. 90–120°.

The monoformoxy compound (IIIa) (115 mg.) was dissolved in 30 ml. of benzene and chromatographed over 9.7 g. of alumina in a column 1.2 cm. in diameter. The column was eluted with 7 ml. portions of solvent as outlined above. The benzene and 4% methanol fraction contained 107 mg. of unchanged 3(α),24-dihydroxy-12(α)-formoxycholane, m. p. 185–186.5.

Saponification of 3(α),24-Dihydroxy-12(α)-formoxycholane (IIIa). The monoformoxy compound (IIIa) (300 mg.) was dissolved in 10 ml. of 5% methanolic sodium hydroxide solution and heated under reflux for ninety minutes. After cooling the solution was diluted with 30 ml. of water and extracted with ether. The ether extract was washed until neutral, dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization of the residue from 3A alcohol and water gave 290 mg. of 3(α),12(α),24-cholantriol (IIIb), m. p. 90–102°.

3(α),12(α),24-triacetoxycholane (IIIc) was formed by acetylating 1 g. of the triol (IIIb) with 15 ml. of acetic anhydride and 15 ml. of pyridine under reflux for two and one-half hours. After three recrystallizations from 3A alcohol and water 640 mg. of product was obtained, m. p. 79.5–80.5°; $[\alpha]^{25}D$ +93.6° (99.4 mg. in 10 ml. chloroform; 1 dcm. tube; α, +0.93°).

Anal. Calcd. for $C_{30}H_{47}O_6$: C, 71.39; H, 9.59; CH_3CO, 25.59. Found: C, 71.43; H, 9.46; CH_3CO, 26.96.

Saponification of 500 mg. of pure 3(α),12(α),24-triacetoxycholane (IIIc), m. p. 79.5–80.5°, yielded 350 mg. of triol, m. p. 100–110°, after repeated crystallizations.

Conversion of 3(α),24-Dihydroxy-12(α)-formoxycholane (IIIa) to Methyl 3-Keto-12(α)-hydroxycholanate (V).—To 100 mg. of IIIa was added 8 ml. of a solution of 1% chromic acid in 95% acetic acid and the resulting solution was allowed to stand at room temperature for thirty minutes. It was then diluted to 40 ml. with water and extracted with 50-ml. of ether, in portions. The ether phase was washed with water and was extracted with 80 ml. of 1% sodium hydroxide solution. The basic extract was acidified with 10% hydrochloric acid and was extracted with 50 ml. of ether. After washing with water and drying over anhydrous sodium sulfate, the ether was removed by evaporation to yield 103 mg. of 3-keto-12(α)-formoxycholanic acid as an oil which was not crystallized.

The oil was dissolved in 20 ml. of 2% ethanolic sodium hydroxide and the solution was refluxed for thirty minutes, cooled, acidified with 10% hydrochloric acid, diluted to four times its volume with water and extracted with 70 ml. of ether. The ether extract was washed with water, dried and evaporated to dryness. The residue, 84 mg., was dissolved in 10 ml. of methanol and 0.2 ml. of acetyl chloride was added. After standing for sixteen hours at room temperature, the solution was diluted to four times its volume with water and extracted with 50 ml. of ether. The ether phase was washed with 30 ml. of 1% sodium hydroxide solution and with water, dried and evaporated to dryness. The residue crystallized on scratching. The yield of methyl 3-keto-12(α)-hydroxycholanate (V) was 72 mg., m. p. 124–139°. Recrystallization from acetone and water, and from acetone and petroleum ether, gave a pure product, m. p. 142–145°. The mixture melting point with an authentic sample showed no depression.

Using the above series of reactions, the following additional conversions to known compounds were made: 100 mg. of the crude aldehyde (probably a mixture of IIa and IIb) gave 59 mg. of V. 221 mg. of methyl 3(α)-hydroxy-12(α)-formoxycholanate (VII) gave 163 mg. of V. 100 mg. of 3(α),12(α),24-trihydroxycholane (IIIb) was oxidized as above to yield 86 mg. of dehydrodesoxycholic acid, m. p. 170–178°. Recrystallized twice from alcohol and water, m. p. 180–184°. An admixture with an authentic sample showed no m. p. depression.

Methyl 3(α),12(α)-Diformoxycholanate.—A solution of 5.0 g. of methyl desoxycholate was heated with 50 ml. of 87% formic acid at 55° for five hours. After diluting with water and working up as usual, crystallization from 170 ml. of 80% alcohol gave 2.8 g. of product, m. p. 78–81°. Two additional crystallizations from the same solvent yielded 2.0 g. of methyl diformyldesoxycholate, m. p. 81.5–82.5°; $[\alpha]^{25}D$ +99° (100 mg. in 10 ml. chloroform, αD, +0.99).

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.03; H, 9.15.

A 250-mg. sample of methyl diformoxycholanate was dissolved in benzene and passed over alumina. The main fraction, consisting of 221 mg. of material, was eluted with benzene +4% methanol and gave an $[\alpha]^{25}D$ of +74°. It was used directly for the oxidation described above.

Summary

1. The Raney nickel desulfurization of thiol esters of desoxycholic acid can be controlled to produce either the corresponding aldehyde or alcohol in good yield.

2. The structures of the resulting products were confirmed by their conversion into known keto derivatives of desoxycholic acid.

3. 3(α),12(α)-Dihydroxycholan-24-al, 3(α),12(α),24-trihydroxycholane, and various derivatives have been characterized.

KALAMAZOO, MICHIGAN RECEIVED DECEMBER 31, 1947

(14) The alumina used in our chromatographic work was "Fisher Adsorption Alumina" obtained from the Fisher Scientific Company and used without further treatment.