DEHYDRATION OF BILE ACIDS AND THEIR DERIVATIVES.
XII. CHOLA-3,7,11-TRIENIC ACID AND ITS PARTIALLY HYDROGENATED COMPOUNDS -- A NOTE ON α-CHOLATRIENIC ACID II

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ABSTRACT

3α-Hydroxychola-7,11-dienic (I), chola-7,11-dienic (II) and 3α,7α-dihydroxychol-11-enic acids (III) were prepared from cholic acid by means of the phosphorus oxychloride procedure. α-Cholatrienic acid II reported by Shimizu et al. (1932) was proved to be identical with chola-3,7,11-trienic acid (IV) which was obtained from I by pyrolytic dehydration. II was prepared through two ways, i.e. (1) through catalytical hydrogenation of IV in neutral medium (2) through dehydration of 7α,12α-dihydroxycholanic acid by means of phosphorus oxychloride. Pyrolysis of 3α-hydroxychol-7-enic acid gave chola-3,7-dienic acid (V). Catalytical hydrogenation of I, II, IV and V (as their methyl esters) in acetic acid gave 7-enic derivatives, and the first three of these were contaminated with more or less amount of the corresponding 7,9--diene derivatives. It is highly probable that γ-cholenic acid obtained by catalytical hydrogenation of α-cholatrienic acid II (Shimizu et al.) is an impure sample of chol-7-enic acid contaminated with chola-7,9-dienic acid. Catalytical reduction of III, as the diacetyl methyl ester, gave methyl 3,7-diacetoxychenodeoxycholate.

The major product of pyrolysis of cholic acid, 3α,7α,12α--trihydroxycholanic acid, is chola-3,6,11-trienic acid[1], which is catalytically reduced into 5β-cholanic acid. In 1932 Shimizu et al.[2] reported on the isolation of a peculiar cholatrienic acid, α-cholatrienic acid II, from the mother liquor of the above-mentioned cholatrienic acid. According to them, on catalytical hydrogenation, it gave β-cholenic acid, chol-8(14)-enic acid[3], in the presence of platinum catalyst, whereas another cholenic acid of unknown structure, γ-cholenic acid, was obtained when palladium catalyst was used.

The properties of γ-cholenic acid, especially of its methyl ester, are very similar to those of chol-7-enic acid and of its ester[4]. If they were of the same structure, Shimizu's acid should be chola-3,7,11-trienic acid*[1], C-7 hydroxyl group of cholic acid being eliminated in the *trans* but not *cis* sense notwithstanding the generally recognized rule of the pyrolytic dehydration.[5]

It had been planned at first that the postulated chola-3,7,11-trienic acid be prepared by pyrolysis of 3α,12α-dihydroxychol-7-enic acid obtained from cholic acid by the phosphorus oxychloride procedure (Berner et al.)[6] It was found, however, that the yield of this dihydroxycholenic acid was rather poor, and that when an excessive amount of phosphorus oxychloride was used according to the procedure of Yamasaki et al.[7], not only C-7 hydroxyl group but also C-12 hydroxyl group of methyl 3α-ethoxycarbonylcholate (Ib)[8] were easily dehydrated to give a product, hydrolysis of which yielded 3α-hydroxychola-7,11-dienic acid (IIa), as will be described below.

This unexpected finding, that the C-12α hydroxyl group of the bile acid is easily eliminated by the phosphorus oxychloride procedure, is reasonably explained by the fact that both C-12α hydroxyl group and C-11β hydrogen are axial and lie in a plane, which provides the conditions susceptible to the trans-elimination.[5] Accordingly, it has been found also that 3α-hydroxychol-11-enic and 3α,7α-dihydroxychol-11-enic acids are obtainable in fairly good yields by the similar treatment of the corresponding 12α-hydroxy bile-acid derivatives. The preparation of the former, an important intermediary compound for the synthesis of the 11-hydroxygenated adrenocortical hormones was reported in the preceding paper of this series.[9] As will be described below, catalytical hydrogenation of the latter 11-enic acid (Xa) gave chenodeoxycholic acid, 3α,7α-dihydroxycholanic acid (XIa), which provides a novel route to the latter from cholic acid.

Pyrolysis of the above-mentioned 3α-hydroxychola-7,11--dienic acid (IIa) gave a cholatrienic acid (IIIa), the physical as well as chemical properties of which are so similar to those of Shimizu's acid,[2] (Table I), as to indicate that they are of the same structure.

Catalytical hydrogenation of the above cholatrienic acid (as the methyl ester, IIIb) in a neutral medium gave methyl choladienate (Vb) of m.p. 105°C. It is highly probable that this choladienate is methyl chola-7,11-dienate, because

TABLE I

	FREE ACID		COLOR REACTION*		METHYL ESTER	
	m.p. °C	αD(Chf.)	LB	TCA	m.p. °C	αD(Chf.)
α-Cholatrienic acid II	169-170	-12.59°	Green	Greenish Blue	103-104	-11.25°
Chola-3,7,11-trienic acid	164-165	-11±1°	Green	Greenish Blue	103-104	-12±1°

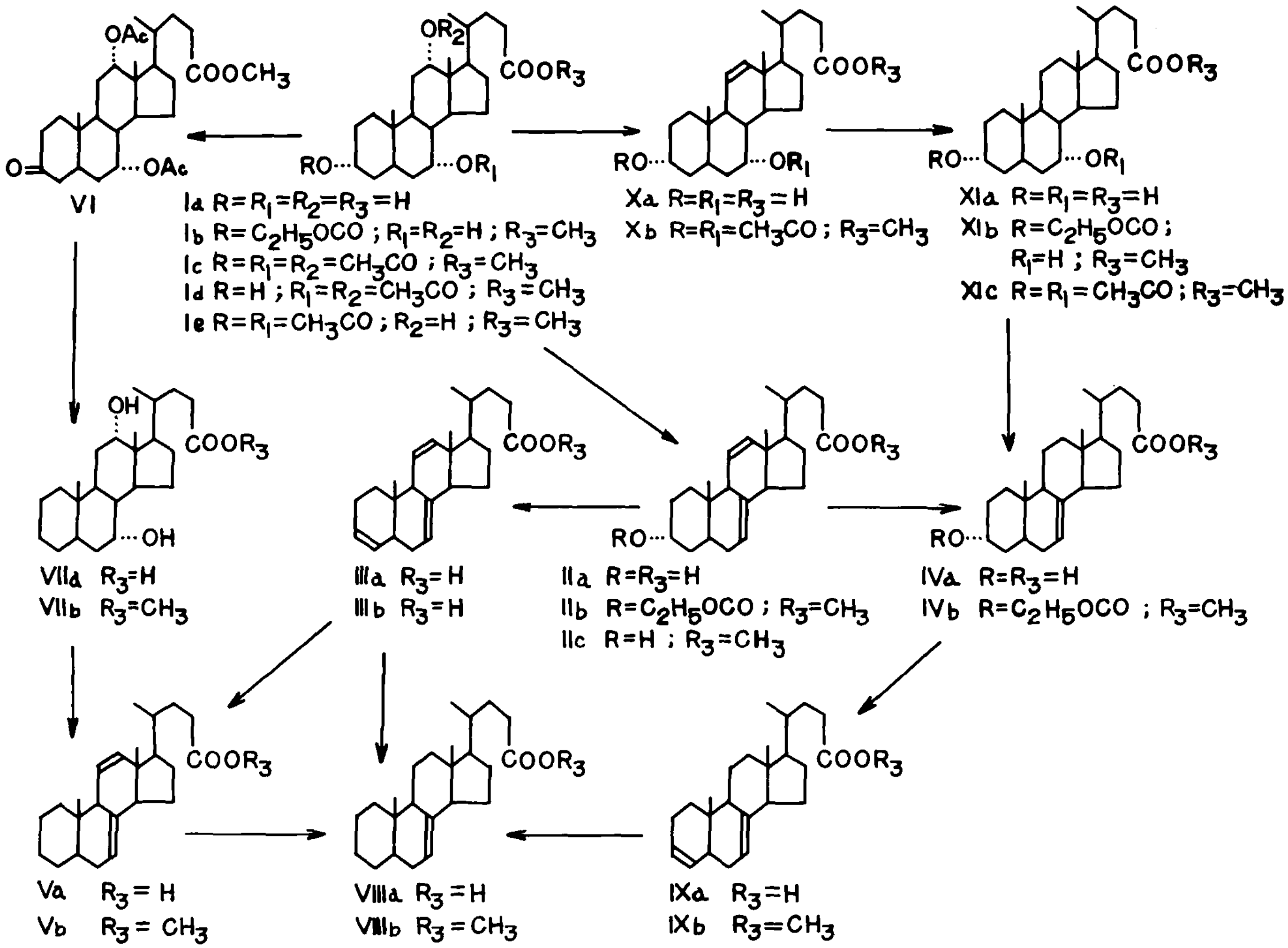
* LB: Liebermann-Burchard reaction.
TCA: Trichloroacetic acid in chloroform.

the same ester was also obtained from methyl ester (VIIb) of 7α,12α-dihydroxycholanic acid by the above dehydrating procedure. The latter bile acid, isodeoxycholic acid[10] was prepared from the 3-oxo-derivative (VI) of cholic acid by Huang-Minlon's method, as will be described below.

The above-mentioned choladienate of m.p. 105°C (Vb) was catalytically reduced to give chol-7-enate, m.p. 95°C (VIIIb), where migration of its 7-ene linkage was not observed. With the use of a platinum catalyst this 7-ene compound was obtainable in a pure state, whereas with use of palladium catalyst it was inseparably contaminated with a compound showing an absorption maximum in the region (244 mμ) which is characteristic of the heteroannular dienes.[11] This compound was later proved to be methyl chola-7,9-dienate,[12] which was also formed, though in a far less amount, when platinum catalyst was used (see in Experimental).

On catalytical hydrogenation followed by hydrolysis, the above-mentioned 3α-ethoxycarbonyloxycholadienate (IIb) gave 3α-hydroxycholenic acid (IVa), m.p. 181°C, which was identical with 3α-hydroxychol-7-enic acid obtained from chenodeoxycholic acid.[13] Pyrolysis of the latter hydroxycholenic acid (IVa) afforded a choladienic acid (IXa), m.p. 136°C, which was quite different from the pyrolysis product of chenodeoxycholic acid, chenocholadienic acid.[1] Catalytical reduction of its methyl ester (IXb) gave methyl chol-7-enate (VIIIb) instead of cholanate. Hence, it can be assumed that the above choladienic acid of m.p. 136°C is chola-3,7-dienic acid.

In a previous paper of this series, it was demonstrated[3] that the double bond of methyl 3α-acetoxychol-7-enate scarcely migrate to the 8,14-position under such conditions as can allow the double bond of each 7-ene compound of 5α-steroids to do so.[14] It is interesting to note, moreover, that when 3α-ethoxycarbonyloxychola-7,11-dienate (IIb), chola-3,7,11-trienate (IIIb), as well as chola-3,7-dienate (IXb) were catalytically hydrogenated into the respective 7-ene derivatives, not only such migration of the 7-ene linkage was not observed at all, but also the first two of these unsaturated acids were partly isomerized, though in a lesser amount, into the 7,9-diene compounds as was the case with the above-


VI
Ia $R=R_1=R_2=R_3=H$
Ib $R=C_2H_5OCO$; $R_1=R_2=H$; $R_3=CH_3$
Ic $R=R_1=R_2=CH_3CO$; $R_3=CH_3$
Id $R=H$; $R_1=R_2=CH_3CO$; $R_3=CH_3$
Ie $R=R_1=CH_3CO$; $R_2=H$; $R_3=CH_3$
Xa $R=R_1=R_3=H$
Xb $R=R_1=CH_3CO$; $R_3=CH_3$
XIa $R=R_1=R_3=H$
XIb $R=C_2H_5OCO$; $R_1=H$; $R_3=CH_3$
XIc $R=R_1=CH_3CO$; $R_3=CH_3$
VIIa $R_3=H$
VIIb $R_3=CH_3$
IIIa $R_3=H$
IIIb $R_3=H$
IIa $R=R_3=H$
IIb $R=C_2H_5OCO$; $R_3=CH_3$
IIc $R=H$; $R_3=CH_3$
IVa $R=R_3=H$
IVb $R=C_2H_5OCO$; $R_3=CH_3$
Va $R_3=H$
Vb $R_3=CH_3$
VIIIa $R_3=H$
VIIIb $R_3=CH_3$
IXa $R_3=H$
IXb $R_3=CH_3$

-mentioned hydrogenation of chola-7,11-dienate.

Fieser and Fieser[14] state that requirements for allylic rearrangement are that the migrating allylic hydrogen be accessible to the catalyst surface and that it can re-enter on the same side of the molecule. If Fieser's statement is true, the failure of the 7-ene linkage of the above compounds of 5β-steroids to migrate to the 8,14--position can be explained by the fact that the above requirements are not fulfilled owing to the special configuration of 5β-steroids. It has been shown,[6] however, that the 7-ene linkage of 3α,12α-dihydroxychol-7-enic acid migrates as those of 5α-steroids do, the resulting product being apocholic acid, 3α,12α-dihydroxychol-8(14)-enic acid. Such an exceptional finding could be due to some favoring influence of C-12α hydroxyl group upon the allylic rearrangement.

EXPERIMENTAL

Preparation of Chola-3,7,11-trienic Acid (IIIa) from Ia. - Methyl 3α-ethoxycarbonyloxychola-7,11-dienate (IIb).

The mixture of methyl 3-ethoxycarbonylcholate[7] (Ib, 5 g, m.p. 176-178°C) and phosphorus oxychloride (25 g) in 50 ml of pyridine was allowed to stand at 50°C for 24 hrs.[9] It was diluted with iced water and extracted thoroughly with ether. The ether extract was washed with dilute hydrochloric acid, water and a 5% solution of sodium carbonate successively, dried over Na_2SO_4 and then evaporated to dryness. Crude crystals, m.p. 90-95°C, were obtained from dilute ethanol. Yield 2 g. Recrystallizations from dilute ethanol gave colorless plates of m.p. 105-108°C, yielding 1.5 g. $[\alpha]_D^{20}$ + 100 ± 1° (Chf.), λmax. 211 mμ (ε_{max}^{EtOH} 2000). Found: C, 72.73; H, 9.11. Calcd. for $C_{28}H_{42}O_5$ (458.644): C, 73.32; H, 9.23%.

3α-Hydroxychola-7,11-dienic acid (IIa).

The above-mentioned ester (IIb, 2.3 g) was dissolved in a 5% alcoholic solution of potassium hydroxide and let stand at room temperature for 24 hrs. The product was precipitated with dilute hydrochloric acid and collected. Yield 1.7 g. The free acid was triturated with acetone and crystallized from dioxane; colorless needles of m.p. 222-224°C, $[\alpha]_D^{18}$ + 93 ± 1°, (Di.); λmax. 211 mμ (ε_{max}^{EtOH} 2500). Found: C, 77.45; H, 9.67. Calcd. for $C_{24}H_{36}O_3$ (372.552): C, 77.37; H, 9.74%.

Methyl chola-3,7,11-trienate (IIIb).

The above acid (IIa, 1.5 g) was heated to 320°C in vacuo (7-8 mm, Hg). The temperature of the sand-bath was maintained at 330°C for less than 5 minutes and then the heating was stopped. The almost colorless distillate obtained was crystallized from acetone-water, yielding 1 g of a crude sample melting at 138-146°C. Methylated with diazomethane as usual, it was dissolved in a small volume of benzene, put on an alumina column (5 g) and eluted with benzene. The eluate was crystallized from ethanol. Several recrystallizations from the same solvent gave colorless plates of m.p. 103-104°C. Yield 500 mg. $[\alpha]_D^{22}$ - 12 ± 1° (Chf.); λmax. 212 mμ (ε_{max}^{EtOH} 2800). (Methyl ester of Shimizu's α-cholatrienic acid II: m.p. 103-104°C, $[\alpha]_D^{20}$ - 11.25°). Found: C, 81.53; H, 9.83. Calcd. for $C_{25}H_{36}O_3$ (368.563): C, 81.47; H, 9.84%.

Chola-3,7,11-trienic acid (IIIa).

The above-mentioned ester (IIIb, 450 mg) was hydrolyzed with a 2% alcoholic solution of potassium hydroxide. The free acid obtained was recrystallized from methanol. Colorless plates of m.p. 164-165°. Yield 300 mg. $[\alpha]_D^{12}$ - 11 ± 1° (Chf.); λmax. 211 mμ (ε_{max}^{EtOH} 3300). (Shimizu's α-cholatrienic acid II: m.p. 169-170°C, $[\alpha]_D^{20}$ - 12.59°). Found: C, 81.38; H, 9.60. Calcd. for $C_{24}H_{34}O_2$ (354.536): C, 81.30; H, 9.66%.

Preparation of 3α-Hydroxychol-7-enic Acid (IVa) from IIb. - Methyl 3α-ethoxycarbonyloxychol-7-enate (IVb).

Methyl 3α-ethoxycarbonyloxychola-7,11-dienate (IIb, 700 mg) dissolved in 20 ml of glacial acetic acid was shaken in hydrogen atmosphere with 200 mg of PtO_2 for 2 hrs. The solution was concentrated in vacuo and diluted with water to give crystalline solid. The crude material showed at first a small, but distinct, absorption band at 244 mμ (ε_{max}^{EtOH} 700) besides the band at 211 mμ (ε_{max}^{EtOH} 2500). Several recrystallizations from methanol afforded a colorless plate of m.p. 135-136°C, $[\alpha]_D^{18}$ + 70 ± 1° (Chf.). λmax. 211 mμ (ε_{max}^{EtOH} 2500). Yield 500 mg. The same so purified showed no more absorption at 244 mμ. Found: C, 73.32; H, 9.44. Calcd. for $C_{28}H_{44}O_5$ (460.660): C, 73.00; H, 9.62%.

3α-Hydroxychol-7-enic acid (IVa).

The above ester (IVb, 300 mg) was hydrolyzed in a 2% alcoholic solution of potassium hydroxide. The free acid obtained was recrystallized from methanol-water. Colorless needles of m.p. 180-181°C (140 mg), undepressed on admixture with an authentic sample prepared by Osawa's procedure.[13] $[\alpha]_D^{25}$ + 62 ± 1° (Chf.). Found: C, 76.79; H, 10.13. Calcd. for $C_{24}H_{38}O_3$ (374.568): C, 76.95: H, 10.22%.

Catalytical Hydrogenation of IIb with Palladium Catalyst.

Methyl 3α-ethoxycarbonyloxychola-7,11-dienate (IIb, 300 mg) dissolved in 10 ml of glacial acetic acid was shaken in hydrogen atmosphere with 300 mg of palladium black for 3 hrs. Several recrystallizations from methanol gave colorless plates of m.p. 134-136°C. Yield 250 mg. $[\alpha]_D^{12}$ + 70 ± 1° (Chf.). Although the physical properties of this sample were quite similar to those of the above-mentioned ester (IVb), it showed, besides the 211 mμ band, a characteristic band at 244 mμ (ε_{max}^{EtOH} ca. 1500) which did not disappear by repeated recrystallization. Recrystallized from acetone-water, the free acid obtained from the ester melted at 173-176°C, undepressed on admixture with an authentic 3α-hydroxychol-7-enic acid (m.p. 181-182°C), and the above-mentioned band at 244 mμ was still observed.

Preparation of Chola-7,11-dienic Acid (Va).

(1) Methyl chola-7,11-dienate (Vb) from IIIb. Methyl chola-3,7,11-trienate (IIIb, 150 mg) in 10 ml of ether was shaken for 2 hrs. in hydrogen atmosphere with 150 mg of PtO_2. Several recrystallizations from methanol gave colorless plates of m.p. 104-105°C, yielding 80 mg., $[\alpha]_D^{17}$ + 83 ± 2° (Chf). λmax. 211 mμ (ε_{max}^{EtOH} 2600). The melting point of this product was not depressed on admixture with an authentic sample of methyl chola-7,11-dienate prepared through the route described below (2). Found: C, 81.13; H, 10.27. Calcd. for $C_{25}H_{38}O_2$ (370.579): C, 81.02; H, 10.33%.

Chola-7,11-dienic acid (Va). The above methyl ester (Vb, 40 mg) in a 3% alcoholic solution of potassium hydroxide was refluxed for 30 minutes. The free acid so obtained was recrystallized from methanol. Colorless needles of m.p. 149-151°C. Yield 25 mg. $[\alpha]_D^{13}$ + 91 ± 8° (Chf.).

(2) Methyl chola-7,11-dienate (VIb) from methyl 7α,12α-dihydroxycholanate (VIIb). - Methyl 3-oxo-7α,12α-diacetoxycholanate (VI). Methyl 3,7,12-triacetylcholate (Ic, 5.4 g) dissolved in methanol (32 ml) containing 1 ml of 35% hydrochloric acid was refluxed on a water-bath for 2 hrs. The reaction product (Id) was extracted with ether and the ether extract was washed with a small volume of water, dried over Na_2SO_4 and then evaporated to dryness. Without further purification the product dissolved in 250 ml of acetone was oxidized with the CrO_3-H_2SO_4 mixture of Bladon et al.[15] Recrystallizations from methanol gave a pure sample of m.p. 191-193°C. Yield 4 g. $[\alpha]_D^{19}$ + 59 ± 2° (Chf). Found: C, 69.14; H, 8.62. Calcd. for $C_{29}H_{44}O_7$ (504.671): C, 69.01; H, 8.78%.

7α,12α-Dihydroxycholanic acid[*2] (VIIa).

The above-mentioned 3-oxo compound (VI, 3.7 g) was reduced according to the modified Huang-Minlon procedure.[16] Recrystallizations from methanol gave colorless needles of m.p. 207-208°C. Yield 2.7 g. $[\alpha]_D^{21}$ + 18 ± 2° (Di.). Found: C, 73.45: H, 10.43. Calcd. for $C_{24}H_{40}O_4$ (392.584): C, 73.42; H, 10.27%.

Methyl ester (VIIb).

The above-mentioned acid (2.3 g) was methylated with an ethereal solution of diazomethane as usual. Recrystallizations from methanol gave colorless needles of m.p. 155-156°C.[*2] Yield 2.3 g $[\alpha]_D^{21}$ + 17 ± 2° (Chf.). Found: C,74.01; H, 10.35. Calcd. for $C_{25}H_{42}O_4$ (406.611): C, 73.84; H, 10.41%.

Methyl chola-7,11-dienate (Vb).

The above-mentioned methyl ester (VIIb, 2g) dissolved in 10 ml of pyridine was dehydrated with phosphorus oxychloride (5 g), exactly as methyl 3-ethoxycarbonylcholate (Ia) was treated. The dehydrated product was recrystallized from methanol. Colorless plates of m.p. 105-107°C. Yield 700 mg. $[\alpha]_D^{17}$ + 82 ± 2° (Chf.). Found: C, 81.32; H, 10.32. Calcd. for $C_{25}H_{38}O_2$ (370.579): C, 81.02; H, 10.33%.

Chola-7,11-dienic acid (Va).

The above-mentioned ester (Vb, 150 mg) was refluxed for 30 minutes with 5 ml of ethanolic potassium hydroxide solution. The reaction mixture was diluted with water and acidified with dilute hydrochloric acid. The crystalline solid was collected and recrystallized from methanol. Colorless needles of m.p. 150-152°C. Yield 130 mg. $[\alpha]_D^{13}$ + 97 ± 1° (Chf.).

This choladienic acid is quite different in nature from ξ-choladienic acid (m.p. 184-185°C), probably chola-6,11-dienic acid, obtained by pyrolysis of 7α,12α-dihydroxycholanic acid.[17]

Preparation of Chol-7-enic Acid (VIIIa).

(1) Methyl chol-7-enate (VIIIb) from Vb. Methyl chola-7,11-dienate (Vb, 200 mg) dissolved in 10 ml of glacial acetic acid was shaken with 100 mg of PtO_2 in hydrogen atmosphere for 4.5 hrs. The reaction product crystallized from dilute ethanol yielded 160 mg. This crude sample (m.p. 89-90°C) showed two distinct absorption bands at 210 and 244 mμ, respectively, the respective extinction quotients (EtOH) being 2200 and 550. The latter, namely the band at 244 mμ, however, was found to disappear upon several recrystallizations from dilute ethanol. Colorless needles; $[\alpha]_D^{18}$ + 65 ± 1° (Chf.). Yield 120 mg. This product melted at 94-95°C, undepressed on admixture with a specimen (m.p. 97-98°C) prepared by Osawa's procedure.[13]

Chol-7-enic acid (VIIIa). The above ester (VIIIb, 70 mg) was hydrolyzed in a 2% alcoholic solution of potassium hydroxide. Recrystallizations from methanol of the free acid so obtained gave colorless prisms of m.p. 150°C. Yield 50 mg. $[\alpha]_D^{19}$ + 65 ± 4° (Chf.). Found: C, 80.09; H, 10.45. Calcd. for $C_{24}H_{38}O_2$ (358.568): C, 80.34; H, 10.68%.

(2) Methyl chol-7-enate (VIIIb) from IIIb. Methyl chola-3,7,11-trienate (IIIb, 40 mg) dissolved in 5 ml of glacial acetic acid was shaken in hydrogen atmosphere with 40 mg of PtO_2 for 4.5 hrs. Several recrystallizations from dilute ethanol gave a sample of m.p. 89-90°C, yielding 25 mg $[\alpha]_D^{18}$ + 56 ± 5° (Chf.); λmax. 211 mμ (ε_{max}^{EtOH} 3500). No depression of the melting point was observed on admixture with an authentic sample of methyl chol-7-enate of Osawa et al.[13] Found: C, 80.58; H, 10.87. Calcd. for $C_{25}H_{40}O_2$ (372.595): C, 80.59; H, 10.82%.

Unlike Shimizu's report, methyl β-cholenate of m.p. 55-56°C could not be obtained, and such discrepancy remains undissolved.

Methyl chola-3,7,11-trienate (IIIb, 500 mg) in 200 ml of glacial acetic acid was shaken in hydrogen atmosphere with 500 mg of palladium black instead of PtO_2 for 1.5 hrs. Several recrystallizations from methanol-acetone gave colorless needles (130 mg). Just like methyl ester of Shimizu's γ-cholenic acid (m.p. 95°C), the product melted at 95-97° and was undepressed on admixture with authentic methyl chol-7-enate. Even though purified by repeated recrystallization, this product showed a distinct absorption band at 244 mμ (ε_{max}^{EtOH} about 1500) which is characteristic of the heteroannular dienes, as did the sample of 3-hydroxychol-7-enic acid obtained from IIb by catalytical hydrogenation with palladium catalyst. Recrystallized from methanol, the free acid obtained from the above ester melted at 136-138°C, $[\alpha]_D^{24}$ 59 ± 3° (Chf.), and the absorption band at 244 mμ had not yet disappeared (Shimizu's γ-cholenic acid: m.p. 137-138°C, $[\alpha]_D^{14}$ + 43.07 (Chf.).

(3) Methyl chol-7-enate (VIIIb) from methyl chola-3,7-dienate (IXb). Chola-3,7-dienic acid (IXa). 3α-Hydroxychol-7-enic acid (IVa) prepared from methyl 3-ethoxycarbonylchenodeoxycholate (XIc)[13] was heated at 290-300°C in vacuo (6-7 mm, Hg). The distillate (1.5 g) was methylated with diazomethane as usual, and let pass through 15 g of alumina column in benzene. The eluate dissolved in a 3% alcoholic solution of potassium hydroxide was let stand at room temperature overnight. Recrystallized from ethyl acetate, the free acid (500 mg) so obtained melted at 138-140°C, $[\alpha]_D^{16}$ + 22 ± 2° (Chf.). The second crop (500 mg) melted at 130-136°C.

Methyl chol-7-enate (VIIIb). The above-mentioned acid (IXa, 200 mg) was methylated with diazomethane as usual. Without being crystallized, the ester (IXb) was dissolved in 10 ml of ether and shaken with 100 mg of PtO_2 in hydrogen atmosphere. Recrystallizations from methanol gave colorless plates (50 mg) of m.p. 94-95°C, $[\alpha]_D^{22}$ + 64 ± 4° (Chf.). The second crop (40 mg) melted at 82-86°C. The same product was also obtained by catalytical hydrogenation of the above methyl chola-3,7-dienate (IXb, 170 mg) in 10 ml of glacial acetic acid, where palladium black was used as catalyst. Recrystallized several times from methanol, the product melted at 94-95°C. Colorless plates; λmax. 215 mμ (ε_{max}^{EtOH} 1100). Found: C, 80.75; H, 10.83. Calcd. for $C_{25}H_{40}O_2$ (372.595): C, 80.59; H, 10.82%.

The melting point of either of the samples obtained as above was not depressed on admixture with authentic methyl chol-7-enate of Osawa.[13]

A Novel Route to Chenodeoxycholic Acid (XIa) from Cholic Acid (Ia). - Methyl 3α,7α-diacetoxychol-11-enate (Xb).

To the solution of methyl 3,7-diacetylcholate[18] (Ie, 4.7 g) in 50 ml of pyridine was added phosphorus oxychloride (15 ml), and the mixture was kept at 50°C for 24 hrs. The reaction mixture was poured cautiously into 500 ml of iced water. The precipitates were collected, washed with water and dried. Crystallized from methanol, the product melted at 126-131°C. Yield 2 g. Several recrystallizations from methanol gave colorless needles of m.p. 139-141°C, $[\alpha]_D^{20}$ + 9 ± 1° (Chf.). The product in acetic acid promptly absorbed bromine and gave a negative result on Beilstein's test for halogen. Found: C, 71.27; H, 9.00. Calcd. for $C_{29}H_{44}O_6$ (488.671): C, 71.29; H, 9.07%.

3α,7α-Dihydroxychol-11-enic acid (Xa).

The above mentioned ester (Xb, 500 mg) was refluxed in 20 ml of a 5% alcoholic solution of potassium hydroxide for 3 hrs. Recrystallized from ethyl acetate, the free acid of colorless blades melted at 204-206°C, $[\alpha]_D^{14}$ + 9 ± 2° (Di.). Yield 380 mg. Found: C, 74.09; H, 9.73. Calcd. for $C_{24}H_{38}O_4$ (390.568): C, 73.80; H, 9.80%.

Methyl diacetylchenodeoxycholate (XIc).

Methyl 3α,7α-diacetoxychol-11-enate (Xb, 500 mg) was subjected to catalytical hydrogenation in acetic acid in the presence of 300 mg of palladium black. Recrystallizations from methanol gave colorless needles of m.p. 129-130°C, $[\alpha]_D^{16}$ + 19 ± 1° (Chf.), yielding 400 mg. No depression of the melting point was observed on admixture with an authentic sample (m.p. 130°C) of methyl diacetylchenodeoxycholate obtained by Hauser's procedure.[19] Found: C, 70.86; H, 9.37. Calcd. for $C_{29}H_{46}O_6$ (490.687): C, 70.98; H, 9.44%.

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FOOTNOTES

*1. Pyrolytic elimination of C-3 hydroxyl group of cholic acid and other bile acids is tentatively assumed to proceed in the same way as is the case with 3α-hydroxycholanic acid.[1]

*2. Isodeoxycholic acid: m.p. 207-208°C. It is very peculiar that the m.p. of its methyl ester in the literature (m.p. 54°C)[10] is far lower than that of the sample here obtained (misprint ?).