122. *Substituted Ketocholanic Acids.*

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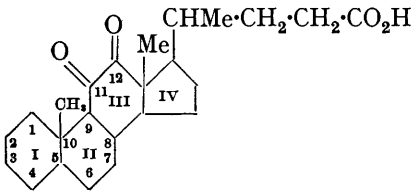
11 : 12-Diketocholanic acid (I) has been converted into the *monosemicarbazone*, and this, with sodium ethoxide, easily yields a *triazine* (II), and not a monoketo-acid.

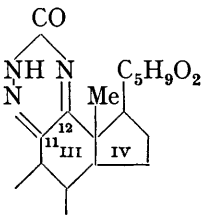
The remarkable formation of 3-hydroxy-7 : 12-diketo- and 3-hydroxy-12-keto-cholanic acids by cold chromic acid oxidation of cholic and deoxycholic acids has been confirmed by conversion of the oxidation products into lithocholic acid. The last substance is thus readily prepared.

IN an attempt to prepare 11-ketocholanic acid (cf. Marker and Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 1334; Barnett and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 926) for comparison with certain natural steroids, the 11 : 12-diketocholanic acid (I) of Wieland and Posternak (*Z. physiol. Chem.*, 1931, **197**, 17) has been investigated. Unlike the 3 : 11-dihydroxy-12-ketocholanic acid of Marker and Lawson (*loc. cit.*), Wieland's acid was easily converted into a *monosemicarbazone*. On hydrolysis, this compound gave the 11-hydroxy-12-keto-$\Delta^{9:11}$-cholenic acid described by Wieland and Posternak (*loc. cit.*).

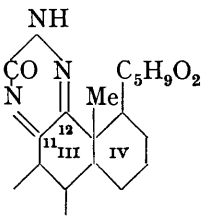
The above semicarbazone, on Kishner–Wollf treatment, readily yielded, not a monoketo-acid, but a substance $C_{25}H_{37}O_3N_3$, which is apparently a *triazine* (II*a* or *b*). With diazomethane, this compound gave a *methyl ester methyl ether*, probably derived from the enolic form C(OH):N· (cf. Bilz, *Annalen*, 1905, **339**, 243; Schmidt and Glatz, *Ber.*, 1911, **44**, 276).



(I.)



(II*a*.)



(II*b*.)

Kaziro and Shimada's claim (*Z. physiol. Chem.*, 1937, **249**, 220) to have converted cholic and deoxycholic acids by direct chromic acid oxidation into 3-hydroxy-7 : 12-diketo- and 3-hydroxy-12-keto-cholanic acid respectively has been confirmed. The oxidation products were readily prepared and both were converted by the usual means into lithocholic acid. These reactions therefore provide a simple route to 3-hydroxy- and substituted 3-hydroxy-cholanic acids.

EXPERIMENTAL.

All m. p.'s are uncorrected. The analyses are microanalyses made by Dr. A. Schoeller.

11 : 12-*Diketocholanic Acid Monosemicarbazone.*—The acid (100 mg.) in ethyl alcohol (10 ml.) was refluxed for 2 hours with a solution of semicarbazide hydrochloride (100 mg.) and crystalline sodium acetate (100 mg.) in water (1·5 ml.). The *semicarbazone* separated in white needles, m. p. 240—242° (decomp.), which were washed with alcohol and dried. Yield, *ca.* 90% (Found : C, 67·0; H, 8·8; N, 9·3. $C_{25}H_{39}O_4N_3$ requires C, 67·4; H, 8·8; N, 9·4%).

Acid hydrolysis. The semicarbazone (50 mg.) was refluxed with methyl alcohol (6 ml.), 2N-sulphuric acid (2 ml.), and concentrated sulphuric acid (12 drops) for 3 hours. The mixture was diluted and extracted with ether, and the residue from the evaporated extract hydrolysed with sodium ethoxide solution (15 ml. of 1%). Acidification of the product, followed by crystallisation of the precipitate from dilute alcohol, gave white crystals, m. p. 140—142° (Found : C, 74·3; H, 9·7%).

Kishner–Wollf treatment. The semicarbazone (75 mg.) was refluxed for 15 minutes, or heated in a sealed tube at 165—175° for 8 hours, with 2 ml. of a solution of sodium (1 g.) in ethyl alcohol (12 ml.). The diluted product was acidified with hydrochloric acid and extracted with ether, and the residue from the washed evaporated extract recrystallised from dilute alcohol. For further purification, a solution of the crystals in alcohol was treated quickly with diazomethane, acidified immediately, diluted, and extracted with ether. The residue from the evaporated extract sublimed at 190—195°/0·05 mm. The gummy product was refluxed for 15 minutes with ethyl alcohol (10 ml.) and 2N-sodium hydroxide (1 ml.). Acidification of the diluted solution, followed by evaporation of its ethereal extract, gave a crystalline residue, which separated from dilute alcohol in long white needles of the *triazine* (II), m. p. 292—295° (decomp.) (Found : C, 70·3, 70·4; H, 8·6, 8·8; N, 9·9, 9·7. $C_{25}H_{37}O_3N_3$ requires C, 70·4; H, 8·7; N, 9·8%).

Treatment of the above triazine with diazomethane, followed by precipitation of the product with water, gave the *methyl ether methyl ester*, which crystallised from methyl alcohol in long white needles, m. p. 142—143° (Found : C, 71·4; H, 9·15; N, 9·3. $C_{27}H_{41}O_3N_3$ requires C, 71·2; H, 9·1; N, 9·2%).

Lithocholic Acid.—(a) *From 3-hydroxy-7 : 12-diketocholanic acid.* Cholic acid (5 g.) in acetic acid (250 ml.) was oxidised at 5—10° with chromic anhydride (2·5 g.) in water (125 ml.) as described by Kaziro and Shimada (*loc. cit.*). After being kept for 16 hours at 0°, the solution was diluted, saturated with sodium chloride, and extracted with ether. The residue from the washed evaporated extract slowly separated from ethyl acetate, containing a little ether, in large crystals (1·7 g.), m. p. 180—182°. These were converted by the usual means into the semicarbazone, and this (0·6 g.) was heated with a saturated solution of sodium ethoxide (5 ml.) in a sealed tube at 180° for 8 hours. Evaporation of a washed ethereal extract of the diluted acidified product left lithocholic acid. A sample of this was converted into methyl 3-acetoxycholanate (below), which was sublimed and hydrolysed; crystallisation of the product from dilute alcohol gave the acid, m. p. 184—185°, $[\alpha]_D^{21°}$ + 36·0° (*c*, 0·56 in ethyl alcohol).

Methyl 3-acetoxycholanate. Methyl lithocholate (30 mg.) was acetylated at 100° for 20 minutes with pyridine (1 ml.) and acetic anhydride (0·5 ml.). The *product*, precipitated with water, crystallised from dilute alcohol in white needles, m. p. 128—130° (Found : C, 74·7; H, 10·3. $C_{27}H_{44}O_4$ requires C, 74·9; H, 10·2%).

(b) *From 3-hydroxy-12-ketocholanic acid.* Deoxycholic acid (10 g.) in acetic acid (700 ml.) and water (50 ml.) was treated at 0—5° with a solution of chromic acid (2·5 g.) in water (25 ml.) and acetic acid (25 ml.), added during 1 hour. After being kept for 16 hours at 0°, the product was carefully diluted with water (1·5 l.), and the precipitated hydrate (7·7 g., m. p. *ca.* 100°) collected and dried. The hydroxyketo-acid formed colourless crystals, m. p. 160—161°, from benzene. The semicarbazone, prepared in the usual way and treated as above with sodium ethoxide, acid, and ether, gave, after one crystallisation from dilute alcohol, lithocholic acid, which, without further purification, had m. p. 178—180° (Found : C, 76·5; H, 10·6%), $[\alpha]_D^{22°}$ + 37·8° (*c*, 0·846 in ethyl alcohol). The methyl ester had m. p. 124—125°, and its acetate m. p. 128—130°. The maximum yield was 3·5 g. of lithocholic acid from 10 g. of deoxycholic acid.

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[*Received, January 28th,* 1939.]