

A New Synthesis of (±)-5:8-Thioctic Acid.

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(±)-5:8-Thioctic acid (I) ($x = 3$; $y = 3$) has been synthesised from 5-ethoxypentan-2-one through 8-ethoxy-5-hydroxyoctanoic lactone (V) and methyl 5:8-dibromo-octanoate (VII).

FOR another investigation a pure sample of (±)-5:8-thioctic acid (I; $x = y = 3$), isomeric with the known growth factor for *Tetrahymena geleii*, (+)-6:8-thioctic acid (I; $x = 2$, $y = 4$), was required. The former acid has previously been synthesised (Reed, Hornberger, Heitmiller, Gunsalus, and Schnakenberg, *J. Amer. Chem. Soc.*, 1953, **75**, 1273; Bullock *et al.*, *ibid.*, 1952, **74**, 3455; 1954, **76**, 1828) but an element of ambiguity existed in the preparation (Reed *et al.*, *loc. cit.*) and a new approach was desirable.

Ethyl 6-ethoxy-3-oxohexanoate (II), prepared from 5-ethoxypentan-2-one with ethyl carbonate and sodium hydride (cf. La Forge and Gersdorf, *J. Amer. Chem. Soc.*, 1948, **70**, 3707), with ethyl acrylate gave diethyl α -(δ -ethoxybutyryl)glutarate (III; R = H) in moderate yield, the main by-product being the bis-addition compound (III; R = CH₂·CH₂·CO₂Et). Acid hydrolysis and decarboxylation of the monoaddition product gave 8-ethoxy-5-oxo-octanoic acid (IV) which was reduced with potassium borohydride in alkaline solution to 8-ethoxy-5-hydroxyoctanoic lactone (V) in high yield. Attempts to convert this lactone into the dithiuronium salt in one stage, by reaction with thiourea and hydrogen bromide in a sealed tube (cf. Reed *et al.*, *loc. cit.*), were unsuccessful and the more circuitous route through 5:8-dibromo-octanoic acid (VI) had to be used. Consistently

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in water (50 ml.) was added portionwise to a cooled solution of 8-ethoxy-5-oxo-octanoic acid (22 g.) in 5*N*-sodium hydroxide (22 ml.) and the mixture set aside for 2 hr. at room temperature. After acidification, the crude lactone was extracted with ether (4 \times 100 ml.). Fractional distillation of the combined, dried extracts gave 8-ethoxy-5-hydroxyoctanoic lactone (12.5 g., 60.9%), b. p. 130—131°/1 mm., n_D^{20} 1.4591 (Found: C, 64.3; H, 9.5. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

Methyl 5:8-Dibromo-octanoate.—Concentrated sulphuric acid (12.5 ml.) was added dropwise to a stirred solution of the above lactone (5 g.) in 25% w/w hydrobromic acid in glacial acetic acid (250 ml.) at 10°. After 18 hr. at room temperature, the mixture was heated at 80° for 8 hr.; a further 10 ml. of 25% w/w hydrobromic acid in glacial acetic acid was added after 4 hr. The cooled, orange mixture was then poured on ice and the crude dibromo-acid extracted with ether (3 \times 100 ml.). The combined, dried ethereal extracts were decolorised by activated charcoal (3 g.) before the addition of diazomethane (2 g.) in ether (100 ml.) (Arndt, *Org. Synth.*, Coll. Vol. II, p. 165). After 2 hr., the excess of diazomethane was destroyed and the solution washed to neutrality with ice-cold sodium hydrogen carbonate solution. Fractional distillation under reduced pressure gave pure *methyl 5:8-dibromo-octanoate* (5.1 g., 76.7%), b. p. 138—140°/1.0 mm., n_D^{21} 1.5083 (Found: C, 34.0; H, 4.96; Br, 50.9. $C_9H_{16}O_2Br_2$ requires C, 34.2; H, 5.1; Br, 50.6%).

(\pm)-5:8-Thioctic Acid.—Methyl 5:8-dibromo-octanoate (4 g.), thiourea (2 g.), and absolute methyl alcohol (50 ml.) were reflux for 8 hr. before removal of the alcohol under reduced pressure. The gummy residue was dissolved in water (25 ml.), and the solution extracted with ether to remove unchanged thiourea (0.2 g.). Removal of the water under a high vacuum gave the methyl octanoate-5:8-dithiuronium dibromide (5.5 g.) as a gum which resisted crystallisation. Addition of sodium picrate (2.5 g.) in water (5 ml.) to the dibromide in water (10 ml.) gave the sparingly soluble *dipicrate*, which crystallised from alcohol as lemon-coloured needles (7.5 g., 78.3%), m. p. 189—192°. This m. p. remained constant throughout a fractional crystallisation (Found: C, 36.05; H, 3.5; N, 17.9. $C_{23}H_{28}O_{16}N_{10}S_2$ requires C, 36.1; H, 3.7; N, 18.3%).

The purified dipicrate (7.5 g.) was added to 2*N*-hydrochloric acid (50 ml.) and the solution successively extracted with ether or chloroform until the liberated picric acid had been extracted. The final traces were removed from the aqueous phase by treatment with activated charcoal.

The following operations were carried out under an inert atmosphere. To the solution of the dichloride was added 30% sodium hydroxide solution (25 ml.) and the whole refluxed for 2 hr. The cooled solution was extracted once with chloroform, acidified with dilute sulphuric acid, and then extracted with ether (4 \times 100 ml.). The combined ethereal extracts were washed once with water and dried before evaporation to dryness under reduced pressure. The residue was dissolved in 5% sodium hydrogen carbonate solution (200 ml.) and treated with 0.1*N*-alcoholic iodine until the colour of iodine persisted for 30 sec. The solution was then acidified to pH 1 with concentrated hydrochloric acid, and the product extracted with ether (4 \times 100 ml.). Evaporation of the ether gave crude (\pm)-5:8-thioctic acid (1.2 g.) as a semi-crystalline magma. Crystallisation from light petroleum (b. p. 40—60°) gave pure (\pm)-5:8-thioctic acid (0.6 g.) as colourless needles, m. p. 57—57.5° (uncorr.). This m. p. could not be further raised by fractional crystallisation from light petroleum and benzene-light petroleum mixtures (Bullock *et al.*, *loc. cit.*, give m. p. 58°) (Found: C, 46.4; H, 6.7; S, 30.9. Calc. for $C_8H_{14}O_2S_2$: C, 46.6; H, 6.8; S, 31%). pK_a' was 6.22 (in 50% ethanol). The infrared spectrum, determined as a mull in Nujol, showed maxima at 2680, 1705, 1419, 1303, 1287, and 935 cm^{-1} .

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