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

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[Reprint Order No. 6475.]

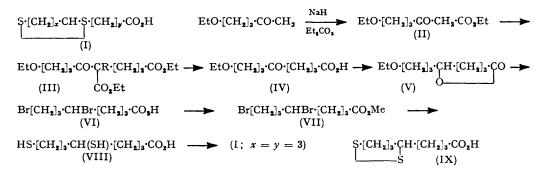
 (\pm) -5: 8-Thioctic acid (I) (x = 3; y = 3) has been synthesised from 5ethoxypentan-2-one through 8-ethoxy-5-hydroxyoctanoic lactone (V) and methyl 5: 8-dibromo-octanoate (VII).

For another investigation a pure sample of (\pm) -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 -ethoxybutyroyl)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

high yields of the dibromo-acid were obtained by treatment of the ethoxy-lactone (V) with hydrogen bromide in glacial acetic acid, in the presence of concentrated sulphuric acid at room temperature and subsequently at 80° (Ames and Bowman, J., 1951, 1079). The crude acid was esterified and the pure methyl ester (VII) obtained. Contrary to the experience of Reed *et al.* (*loc. cit.*) no evidence of lactonisation or rearrangement of the dibromo-ester (VII) was observed, the product appearing homogeneous in both its physical and subsequent chemical behaviour. The final stages of the synthesis, through the dithiuronium salt, were carried out substantially as described by Reed *et al.* (*loc. cit.*). The dithiuronium bromide could not be crystallised, but conversion into the dipicrate gave a high-melting material, which was readily crystallised. Alkaline hydrolysis of the corresponding dichloride gave 5:8-dimercapto-octanoic acid (VIII) which was cyclised to (\pm) -5:8-thioctic acid (IX) in poor yield.

Contrary to expectation, the (\pm) -5: 8-thioctic acid did not give, in our hands, a positive sodium nitroprusside test for a thiol group in the presence of sodium cyanide. This



abnormal behaviour can presumably be attributed to the greater stability of the sixmembered ring system, compared with the five-membered ring system in (\pm) -6:8thioctic acid.

EXPERIMENTAL

Ethyl 6-Ethoxy-3-oxohexanoate.—5-Ethoxypentan-2-one (70 g.), b. p. $70-72^{\circ}/10$ mm. (Harradence and Lions, J. Proc. Roy. Soc. New South Wales, 1940, 74, 159), in anhydrous ether (70 ml.) was added to a stirred suspension of powdered sodium hydride (26 g.) in anhydrous ether (200 ml.) and ethyl carbonate (200 g.), the rate of addition being adjusted to maintain a steady reflux. When the exothermic reaction had subsided, the mixture was refluxed for a further 2 hr. The excess of sodium hydride was then decomposed by the addition of absolute ethanol (5 ml.) and the mixture poured into an excess of dilute hydrochloric acid. The etheral phase was washed with 5% sodium hydrogen carbonate solution, dried, and fractionally distilled, to give ethyl 6-ethoxy-3-oxohexanoate (86 g., 79%), b. p. 89—91°/1 mm., n_D^{20} 1.4335 (Found : C, 59.5; H, 8.9. C₁₀H₁₈O₄ requires C, 59.4; H, 9.0%).

Ethyl α-(δ-*Ethoxybutyroyl*)glutarate.—Freshly distilled ethyl acrylate (14 g.) was added dropwise, during 1 hr., to a stirred solution of 10% alcoholic potassium hydroxide (5 ml.) in ethyl 6-ethoxy-3-oxohexanoate (50 g.) at 120° and the temperature kept thereat for a further hour. The mixture was poured into an excess of dilute hydrochloric acid and the product extracted with ether (4 × 100 ml.). Fractional distillation under reduced pressure gave the pure glutarate (39 g., 53·4%), b. p. 120–122°/0·2 mm., n_D^{21} 1·4441 (Found : C, 59·5; H, 8·7. C₁₅H₂₆O₆ requires C, 59·6; H, 8·7%), and *ethyl* 8-ethoxy-4-ethoxycarbonyl-4·2'-ethoxycarbonylethyl-5-oxooctanoate (7 g.), b. p. 172–173°/0·2 mm., n_D^{20} 1·4534 (Found : C, 59·6; H, 8·4. C₂₀H₃₄O₈ requires C, 59·7; H, 8·5%).

8-Ethoxy-5-oxo-octanoic Acid.—Refluxing the foregoing diester (39 g.) with sulphuric acid (40 g.) in 50% w/w acetic acid (160 g.) for 2 hr. gave 8-ethoxy-5-oxo-octanoic acid (22 g., 84·3%), b. p. 160°/0·1 mm., n_{20}^{20} 1·4545 (Found : C, 59·4; H, 8·8%; equiv., 201. C₁₀H₁₈O₄ requires C, 59·4; H, 9·0%; equiv., 202·2).

8-Ethoxy-5-hydroxyoctanoic Lactone.—An ice-cold solution of potassium borohydride (8 g.)

in water (50 ml.) was added portionwise to a cooled solution of 8-ethoxy-5-oxo-octanoic acid (22 g.) in 5N-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. C₁₀H₁₈O₃ 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 × 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., $n_{\rm D}^{21}$ 1·5083 (Found : C, 34·0; H, 4·96; Br, 50·9. C₉H₁₆O₂Br₂ requires C, 34·2; H, 5·1; Br, 50·6%).

 (\pm) -5: 8-Thiotic 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 2N-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 (4×100 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 0-1N-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 (4×100 ml.). Evaporation of the ether gave crude (\pm)-5 : 8-thioctic acid (1·2 g.) as a semi-crystalliane 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 C₈H₁₄O₂S₂ : 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.

The author thanks Dr. R. E. Bowman for advice and help, Miss E. M. Tanner for physical measurements, and Mr. A. J. Durre for the microanalyses.

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