594. *A New Synthesis of* 6 : 8-*Thioctic Acid.*

By E. A. BRAUDE, R. P. LINSTEAD, and K. R. H. WOOLDRIDGE.

6 : 8-Thioctic acid (I) has been synthesised by a new route starting from hept-6-enoic acid.[1] A Prins reaction with paraformaldehyde yields a mixture of 6 : 8-methylenedioxyoctanoic acid (II; R = H) and 6 : 8-diacetoxyoctanoic acid (III; R = H) which is converted into methyl 6 : 8-dihydroxyoctanoate (IV; R = Me) and thence by known methods into 6 : 8-thioctic acid (five stages; overall yield 20—30%). Alternatively, the products of the Prins reaction can be converted directly into thioctic acid (three stages; overall yield 8%).

THE cyclic disulphide, 6 : 8-thioctic acid (I), was first isolated [2] in 1951 from liver and has been shown to fulfil a number of important biological functions, including those of growth-factor (" protogen ") for certain bacteria and of co-enzyme (" lipoic acid ") for the oxidative decarboxylation of pyruvate. More recently, it has been suggested [3] that 6 : 8-thioctic acid plays the part of hydrogen acceptor in the primary step of photosynthesis. In connection with experiments on photochemical hydrogen-transfer in model systems, we required a supply of 6 : 8-thioctic acid. Since none of the methods of synthesis [4-6] known at the time appeared particularly convenient, we devised a new route which is described in this

---

[1] Braude, Linstead, and Wooldridge, *Chem. and Ind.*, 1955, 508; Braude, Proceedings of " Symposium su l'acido tioctico," Naples, November, 1955.

[2] Reed, DeBusk, Gunsalus, and Hornberger, *Science*, 1951, **114**, 93; Reed, Gunsalus, Schnakenberg, Soper, Boaz, Kern, and Parke, *J. Amer. Chem. Soc.*, 1953, **75**, 1267; Patterson, Pierce, Stokstad, Hoffmann, Brockman, Day, Macchi, and Jukes, *ibid.*, 1954, **76**, 1823.

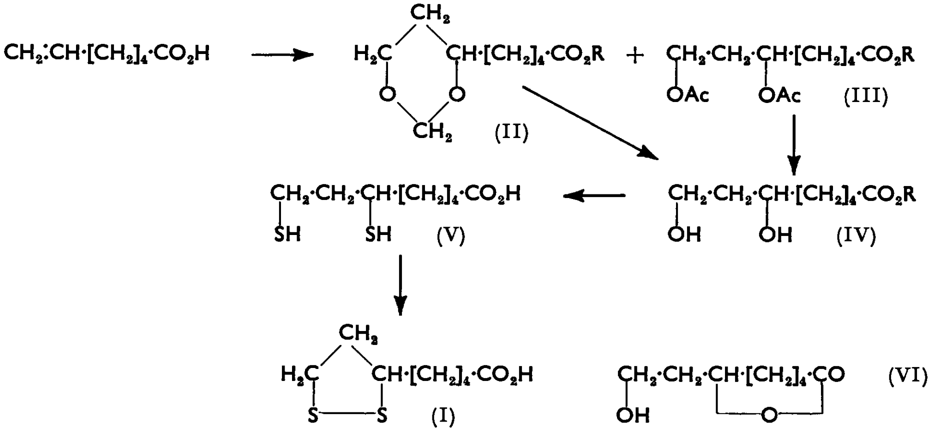
[3] Calvin and Barltrop, *ibid.*, 1952, **74**, 6153; Barltrop, Hayes, and Calvin, *ibid.*, 1954, **76**, 4348.

[4] Hornberger, Heitmiller, Gunsalus, Schnakenberg, and Reed, *ibid.*, 1953, **75**, 1273.

[5] Bullock, Brockman, Patterson, Pierce, Saltza, Sanders, and Stokstad, *ibid.*, 1954, **76**, 1828.

[6] Soper, Buting, Cochran, and Pohland, *ibid.*, p. 4109.

paper. Starting from hept-6-enoic acid, it affords a 20—30% overall yield of 6 : 8-thioctic acid in five stages, or 8% in only three stages. The best previous method[5] gave about 8% in six stages from δ-chloroformylvalerate, but in the meantime this has been much improved by Reed and Niu[7] and thioctic acid is now available commercially. A further synthesis which gives a low yield but permits the preparation of the optically active forms of the acid has also been published.[8]



Hept-6-enoic acid was prepared by two methods : from tetrahydrofurfuryl alcohol by way of 5-bromopent-1-ene and pent-4-enylmalonic ester[9] or from tetrahydrofuran by way of 1-bromo-4-chlorobutane and hept-6-ynoic acid,[10] with slight modifications of the procedures previously described. On a large scale, the first method was the more convenient. Addition of formaldehyde to hept-6-enoic acid proceeded readily in the presence of sulphuric acid in anhydrous acetic acid. A mixture of two products, evidently 6 : 8-methylenedioxyoctanoic acid (II; R = H) and 6 : 8-diacetoxyoctanoic acid (III; R = H) in a ratio of about 5 : 1 was obtained. Both types of products have also been encountered in other cases.[11] The two acids were not easily separated, but their methyl esters were obtained pure by fractionation. Reaction of ethyl hept-6-enoate with formaldehyde under similar conditions afforded a lower yield of the ethyl ester (II; R = Et), while ethyl undecenoate, for comparison, gave a mixture analogous to that obtained from heptenoic acid. The only other example of a Prins reaction with an unsaturated acid or ester appears to be that reported by Pigulevskii and Tatarskaya,[12] who obtained a 4% yield of an addition product of uncertain constitution by treating oleic acid with aqueous formaldehyde and sulphuric acid.

Direct acid hydrolysis of the Prins reaction product from hept-6-enoic acid did not afford the desired 6 : 8-dihydroxyoctanoic acid (IV; R = H) but mainly a substance derived from it by the loss of one molecular proportion of water. This is evidently the ε-lactone (VI) since the infrared spectrum shows the presence of a hydroxyl, but absence of a free carboxyl group; the carbonyl stretching frequency (1730 $cm.^{-1}$) is very close to that shown by long-chain esters.[13] Though few analogous cases have been examined, the apparent ease of formation of the lactone (VI) is not unexpected;[14] thus, 6-hydroxyoctanoic

---

[7] Reed and Ching-I Niu, *J. Amer. Chem. Soc.*, 1955, **77**, 416.

[8] Walton, Wagner, Bachelor, Peterson, Holly, and Folkers, *ibid.*, p. 5144.

[9] Gaubert, Linstead, and Rydon, *J.*, 1937, 1971.

[10] Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4263.

[11] Arundale and Mikeska, *Chem. Rev.*, 1952, **51**, 505; Nenitzescu and Przemetzky, *Ber.*, 1941, **74**, 676.

[12] Pigulevskii and Tatarskaya, *Zhur. obschei Khim.*, 1950, **20**, 1456; *Chem. Abs.*, 1951, **45**, 2480.

[13] Thompson and Torkington, *J.*, 1945, 640; O'Connor, Field, and Singleton, *J. Amer. Oil Chemists' Soc.*, 1951, **28**, 154.

[14] (*a*) Blaise, *Compt. rend.*, 1909, **148**, 1773; *Bull. Soc. chim. France*, 1910, **7**, 411; (*b*) Marvel, McCorquodale, Kendall, and Lazier, *J. Amer. Chem. Soc.*, 1924, **46**, 2838; Marvel and Birkhimer, *ibid.*, 1929, **51**, 260.

acid lactonises when heated.* Lactonisation was avoided by first converting the mixture of acids into the methyl esters (II and III; R = Me) and then conducting the acid hydrolysis in excess of methanol so that the methoxycarbonyl group was preserved. In this way, an excellent yield of methyl 6 : 8-dihydroxyoctanoate (IV; R = Me) (83% from heptanoic acid) was obtained.

The dihydroxy-ester was heated with thiourea and hydrogen iodide [5, 15] and then hydrolysed by alkali, yielding directly 6 : 8-dimercapto-octanoic acid (V). The average yield in this reaction was only 30% and could not be raised by varying the conditions or by treating the crude product with sodium in liquid ammonia to reduce any polymeric sulphide formed. The final stage, oxidation of the dithiol to 6 : 8-thioctic acid, was effected almost quantitatively with iodine, or oxygen and ferric chloride, following known procedures.[5] The synthesis can be shortened by carrying out the thiourea–hydrogen iodide reaction directly on the crude product of the Prins reaction, but the overall yield is appreciably lower, probably owing to the formation of the lactone (VI) under the acidic conditions.[16] A third variant, which has no practical advantage, involves the conversion of the dihydroxy-ester (IV; R = Me) into the dithiol (V) by successive toluene-*p*-sulphonylation, treatment with potassium thiolacetate,[17] and alkaline hydrolysis.

EXPERIMENTAL

Analytical data were determined in the microanalytical (Mr. F. H. Oliver and staff) and spectroscopic (Mr. R. L. Erskine and Mrs. A. I. Boston) laboratories of this Department. M. p.s were determined on a Kofler apparatus and are corrected. All solutions were dried over anhydrous sodium sulphate.

Hept-6-enoic Acid.—This was best prepared by the method of Gaubert, Linstead, and Rydon.[9] 1-Bromopent-4-ene [18] (206 g.; b. p. 132—134°, n_D^{23} 1·4657) was added during 0·5 hr. to a stirred solution obtained from ethanol (385 ml.), sodium (38·5 g.), and diethyl malonate (324 g.). The mixture was stirred for 16 hr. at room temperature and then worked up in the usual way, giving diethyl pent-4-enylmalonate (271 g., 85%), b. p. 134°/14 mm. The ester was hydrolysed when stirred overnight with water (250 ml.), ethanol (50 ml.), and potassium hydroxide (400 g.), and the crude acid, m. p. 86—88°, obtained on acidification with sulphuric acid and extraction with ether was decarboxylated by slow distillation at 160°/20 mm. Fractionation through a short column gave hept-6-enoic acid (112 g., 75%), b. p. 74°/0·5 mm., n_D^{20} 1·4388 (Gaubert *et al.*[9] give b. p. 125°/15 mm., n_D^{15} 1·4404). Infrared light absorption (liquid film): bands at 2667 (medium, O–H stretching), 1808 (weak, $CH_2=$ bending overtone), 1709 (strong, C=O stretching), 1639 (weak, C=C stretching), 1287, 1236 (strong), 992 and 909 (medium, $CH_2=$ bending) cm.$^{-1}$.

Hept-6-enoic acid and the ethyl ester were also obtained from hept-6-ynoic acid,[10] but this method was less convenient on the scale required. Hept-6-ynoic acid (25 g.), b. p. 92°/0·5 mm., n_D^{22} 1·4514, and 5% palladium–charcoal (1·0 g.) were shaken in hydrogen until 4600 ml. at 16°/761 mm. had been taken up. Distillation gave hept-6-enoic acid (20 g., 79%), b. p. 85°/1 mm., n_D^{21} 1·4387.

Hept-6-ynoic acid (32 g.), ethanol (27 ml.), benzene (50 ml.), and sulphuric acid (3 ml.) were heated under reflux for 40 hr. The mixture was worked up in the usual way, giving *ethyl hept-6-ynoate* (30 g., 76%), b. p. 94°/20 mm., n_D^{22} 1·4357 (Found: C, 70·3; H, 9·3. $C_9H_{14}O_2$ requires C, 70·2; H, 9·1%). The ester (15 g.), ethyl acetate (35 ml.), and 5% palladium–charcoal (1 g.) were shaken in hydrogen until 2400 ml. at 23°/761 mm. had been taken up. Distillation gave ethyl hept-6-enoate (11·5 g., 77%), b. p. 85°/30 mm., n_D^{23} 1·4235.

---

* Further work (Braude, Elvidge, and Mahmoud, unpublished) shows that the acetyl derivative of the lactone (VI) is a neutral product of the Prins reaction. The formation of (VI) can be regarded as an intramolecular cyclisation of the intermediate carbonium ion $HO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{C}H{\cdot}[CH_2]_4CO_2H$ which competes with the reactions of the ion with formaldehyde to give (II), or with acetic acid to give (III).

[15] Frank and Smith, *J. Amer. Chem. Soc.*, 1946, **68**, 2103.

[16] Campbell, *J.*, 1955, 4218, has recently reported a similar failure of the thiourea reaction with the lactone of 8-ethoxy-5-hydroxyoctanoic acid.

[17] Chapman and Owen, *J.*, 1950, 579.

[18] Brooks and Snyder, *Org. Synth.*, Coll. Vol. III, p. 698; LaForge, Green, and Gersdorff, *J. Amer. Chem. Soc.*, 1948, **70**, 3707.

Prins Reaction with Hept-6-*enoic Acid.*—Hept-6-enoic acid (50 g.) was added dropwise during 45 min. to a stirred mixture of acetic acid (200 ml.), acetic anhydride (3 ml.), sulphuric acid (20 ml.), and paraformaldehyde (40 g.) at 40°. Sitrring was continued for 15 hr. at room temperature and then for 2 hr. at 90—100°. The resulting clear solution was cooled to 0° and slowly poured into ice-water (2 l.), and the mixture was extracted with chloroform. The chloroform solution was dried and evaporated and the amber-coloured residue was heated at 100°/20 mm. to remove acetic acid. The remaining liquid (90 g.) was taken up in excess of saturated aqueous sodium hydrogen carbonate, and the solution was extracted with ether to remove traces of non-acidic products, treated with charcoal, acidified with 2N-hydrochloric acid, and extracted with chloroform. The chloroform solution was dried and fractionated, giving a mixture (82·5 g.) of 6 : 8-methylenedioxyoctanoic acid (II; R = H) and 6 : 8-diacetoxyoctanoic acid (III; R = H), b. p. 166—174°/0·1 mm., n_D^{24} 1·4650—1·4670 (Found: equiv., 226—247. Calc. for $C_9H_{16}O_4$: equiv., 118. Calc. for $C_{12}H_{20}O_6$: equiv., 260). The lower-boiling fractions were almost pure 6 : 8-*methylenedioxyoctanoic acid* (Found: C, 57·4; H, 8·2. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%).

The mixed acids (10 g.) were treated with excess of diazomethane in ether. Fractionation afforded *methyl* 6 : 8-*methylenedioxyoctanoate* (II; R = Me) (5·4 g.), b. p. 112°/10^{-2} mm., n_D^{22} 1·4519 (Found: C, 59·2; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%), and *methyl* 6 : 8-*diacetoxyoctanoate* (III; R = Me) (1·0 g.), b. p. 140° (bath-temp.)/10^{-4} mm., n_D^{23} 1·4625 (Found: C, 56·8; H, 8·0. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1%). Infrared light absorption of the latter (liquid film): strong bands at 1748 (C=O stretching), 1244 and 1038 (acetate) cm.$^{-1}$.

Another portion of the mixture of acids (25 g.) was hydrolysed by 2N-sulphuric acid (100 ml.) and ethanol (20 ml.) at 100° for 4 hr. Removal of the ethanol, addition of 2N-sodium hydroxide (150 ml.), heating at 100° for a further 4 hr., acidification and continuous ether-extraction for 15 hr. gave an extract which was dried and fractionated, giving impure 6 : 8-*dihydroxyoctanoic* 6-*lactone* (VI) (8·5 g.), b. p. 140° (bath-temp.)/10^{-4} mm., n_D^{22} 1·4738 (Found: C, 59·8; H, 8·8. $C_8H_{14}O_3$ requires C, 60·75; H, 8·9%). Infrared light absorption (liquid film): strong bands at 1730 (C=O stretching) and 3436 cm.$^{-1}$ (O–H stretching).

Prins Reaction with Ethyl Hept-6-*enoate.*—Ethyl hept-6-enoate (b. p. 80°/18 mm.; 11 g.) was added dropwise at 0° to a stirred mixture of paraformaldehyde (4·2 g.), acetic acid (27 g.), acetic anhydride (0·5 ml.), and sulphuric acid (3 ml.). The mixture was kept at 30—35° for 20 hr., diluted with water, and extracted with ether. The ether extract was washed successively with water, sodium hydrogen carbonate solution, and water, dried, and distilled, giving a mixture (8 g.), b. p. 70—140°/0·5 mm., n_D^{22} 1·430—1·451. Refractionation of the middle cuts afforded *ethyl* 6 : 8-*methylenedioxyoctanoate*, b. p. 120°/0·5 mm., n_D^{22} 1·4492 (Found: C, 60·7; H, 9·0. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%).

Prins Reaction with Ethyl Undecenoate.—Ethyl undecenoate (b. p. 95°/1·5 mm.; 10 g.) was added dropwise to a stirred mixture of paraformaldehyde (4·2 g.), acetic acid (27 g.), and sulphuric acid (4·2 g.). The mixture was kept at 30—35° for 24 hr. and then heated to 65° for a few minutes, to give a clear solution. This was diluted with water and extracted with ether, and the ether extract was treated as above, giving a mixture (6 g.), b. p. 160—170°/0·5 mm., n_D^{23} 1·4600—1·4655 (Found: C, 64·3; H, 9·6. Calc. for $C_{15}H_{28}O_4$: C, 66·2; H, 10·3. Calc. for $C_{18}H_{32}O_6$: C, 62·8; H, 9·3%).

Methyl 6 : 8-*Dihydroxyoctanoate* (IV; R = Me).—Crude product (118 g.) from the Prins reaction of heptenoic acid (62 g.) was treated with excess of diazomethane in ether. The solvent was removed and the mixture of esters heated under vigorous reflux with dry methanol (1 l.) and sulphuric acid (5 ml.) under a Fenske column fitted with a total condensation take-off head operating at a reflux ratio of 40 : 1, so that methyl acetate and dimethoxymethane were continually removed. Additional methanol was added at intervals to maintain the volume. After 24 hr., only pure methanol distilled and the solution was cooled, neutralised with a slight excess of aqueous sodium hydrogen carbonate, concentrated under reduced pressure to remove methanol, diluted with water, acidified with hydrochloric acid, and extracted with ether. From the extract, unchanged ester (18 g.) was recovered.

The aqueous solution was again neutralised with sodium hydrogen carbonate and then concentrated at 100°/20 mm. The semisolid residue was extracted three times with boiling chloroform, and the extract was fractionated, giving *methyl* 6 : 8-*dihydroxyoctanoate* (65 g., 83% from heptenoic acid allowing for recovered ester), b. p. 110—115° (bath-temp.)/10^{-4} mm., n_D^{22} 1·4667 (Found: C, 56·8; H, 9·3. $C_9H_{18}O_4$ requires C, 56·8; H, 9·5%). Infrared light absorption (liquid film): strong bands at 3448 (O–H stretching), 1736 (C=O stretching), 1256, 1202, 1160, 1095 (secondary C–O stretching), 1055 (primary C–O stretching), 1001, and 970 cm.$^{-1}$.

6 : 8-*Thioctic Acid* (I).—*First method* (cf. ref. 5). Crude methyl 6 : 8-dihydroxyoctanoate (20 g.), thiourea (60 g.), and 55% hydriodic acid (150 g.) were heated under reflux for 24 hr. After cooling, potassium hydroxide (90 g.) in water (300 ml.) was added and the mixture was refluxed for 12 hr. under nitrogen. It was then extracted with ether, acidified with 2N-hydrochloric acid, and extracted with chloroform. The chloroform was removed and the residue (11·5 g.) was dissolved in liquid ammonia (*ca.* 100 ml.). Sodium (1 g.) was added in small pieces until a permanent blue colour remained. The colour was then discharged by the addition of solid ammonium chloride, and the ammonia was allowed to evaporate overnight. The residue was dissolved in water, acidified with hydrochloric acid, and extracted with chloroform. The extract was dried and distilled, giving 6 : 8-dimercapto-octanoic acid (6·0 g.), b. p. 140—146°/0·1 mm., n_D^{22} 1·5228. This, on oxidation with ferric chloride and oxygen[5] afforded DL-6 : 8-thioctic acid (5·2 g., 19·6% based on heptenoic acid), which crystallised from light petroleum (b. p. 40—60°) as yellow crystals, m. p. 60°, $\lambda_{\max.}$ 3330 Å (ε 230 in CCl_4), 3320 Å (ε 150 in EtOH) (Found : C, 46·9; H, 6·9; S, 30·5. Calc. for $C_8H_{14}O_2S_2$: C, 46·6; H, 6·8; S, 31·1%). The m. p. was undepressed on admixture with a specimen kindly supplied by Dr. L. J. Reed. This represents a typical run; the yield of the thiourea–hydriodic acid reaction varied considerably under apparently identical conditions and overall yields of up to 32% were attained on a smaller scale.

Second method. The crude mixed acids (9·3 g.) from the Prins reaction on hept-6-enoic acid were heated with thiourea (15 g.) and 55% hydriodic acid (45 ml.) for 65 hr. After cooling, sodium hydroxide (50 g.) in water (50 ml.) was added and the mixture was refluxed under nitrogen for 6 hr. It was then extracted with ether, acidified with 2N-sulphuric acid, and extracted with chloroform. The extract was dried and the solvent removed. Distillation of the yellow oil (4·6 g.) which remained afforded 6 : 8-dimercapto-octanoic acid (1·5 g.), b. p. 150—162°/10^{-2} mm. (Found : S, 29·8%). Oxidation as above gave 6 : 8-thioctic acid (1·1 g., 8·4% based on heptenoic acid), m. p. 60°.

Third method (cf. ref. 17). Methyl 6 : 8-dihydroxyoctanoate (6·5 g.) in pyridine (10 ml.) was added dropwise at 0° to a stirred solution of toluene-*p*-sulphonyl chloride (20 g.) in pyridine (20 ml.), and the mixture was kept at 0° for 18 hr. Ice-water (20 ml.) was then added and the mixture shaken with freshly distilled chloroform (100 ml.). The chloroform layer was separated, extracted repeatedly with N-sulphuric acid, washed with water, and dried. Removal of the solvent gave an oil (10·8 g.) which deposited a small amount of solid at 0°. The solid was separated and crystallised from methanol–light petroleum (b. p. 60—80°) to give the *mono-toluene-*p*-sulphonyl derivative*, m. p. 80—82° (Found : C, 56·4; H, 6·9; S, 9·3. $C_{16}H_{24}O_6S$ requires C, 55·8; H, 7·0; S, 9·3%).

The crude ditoluene-*p*-sulphonate, potassium thiolacetate (6 g.), and acetone ("AnalaR"; 50 ml.) were heated under vigorous reflux for 14 hr. The mixture was cooled to 0° and the solid (8·2 g.) which separated was filtered off and washed with acetone. The acetone solution and washings were evaporated and the residue was dissolved in ether. The ether solution was extracted with water, dried, and distilled, giving impure methyl 6 : 8-diacetylthio-octanoate (4·5 g.), b. p. 135—140° (bath-temp.)/5 × 10^{-3} mm., n_D^{21} 1·5075 (Found : S, 18·0. Calc. for $C_{13}H_{22}O_4S_2$: S, 21·0%).

The diacetyl derivative was refluxed under nitrogen with 2N-potassium hydroxide (35 ml.) until the mixture was homogeneous (90 min.). The solution was cooled, acidified with 2N-sulphuric acid, and extracted with chloroform. The extract was dried and evaporated, giving a pale yellow oil (2·0 g.) which was dissolved in aqueous sodium hydrogen carbonate (100 ml.). A dilute solution of iodine in aqueous potassium iodide was added until a permanent colour remained. The colour was discharged by a few drops of aqueous sodium thiosulphate and the mixture was acidified and extracted with chloroform. The chloroform extract was dried and distilled, giving as the main product (0·30 g., 4% from methyl 6 : 8-dihydroxyoctanoate) a fraction, b. p. 140° (bath-temp.)/5 × 10^{-4} mm., which solidified and then had m. p. 44—48°. Crystallisation from light petroleum (b. p. 40—60°) afforded 6 : 8-thioctic acid, m. p. 60°.

The work described in this paper was carried out during the tenure by one of us (K. R. H. W.) of a Beit Research Fellowship which is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.
[*Received, March* 24*th*, 1956.]