[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF FARMOCHIMICA CUTOLO-CALOSI S.P.A.]

A New Synthesis of 6-Thioctic Acid (DL-α-Lipoic Acid)

BY AUGUSTO SEGRE, RENE VITERBO AND GIOVANNI PARISI

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6-Thioctic acid has been synthesized starting from 2-acetoxyethylcyclohexanone by peracid oxidation to the 1 → 6-lactone of 6-hydroxy-8-acetoxyoctanoic acid and reaction, with thiourea and a strong mineral acid, of this lactone, followed by alkaline hydrolysis of the isothiuronium salt and oxidation of the dithiol-acid thus formed. A preparation of 2-acetoxyethylcyclohexanone, starting from cyclohexanone, is also described.

The importance of 6-thioctic acid (VII) in biochemical processes is well known.[1] Thus its clinical application in the therapy of liver diseases[2] and its antitoxic activity combined with its low toxicity[3] have promoted many syntheses.[1,4] The synthetic method of preparation described in the present paper has the characteristics of starting from easily available raw materials, of using inexpensive reagents in simple reactions and of obtaining comparatively high yields.

The first object of a synthesis of 6-thioctic acid (VII) is to obtain a carboxylic acid with a normal chain of eight carbon atoms, with substituents at C_6 and C_8 suitable for the introduction of two thiol groups. The 1→6-lactone of 6-hydroxy-8-acetoxyoctanoic acid (V) is, in this sense, the required substance. Its preparation is a clear case for the application of the well known Baeyer–Villiger peracid ketone oxidation.[5] Indeed we have obtained the lactone V by peracetic acid oxidation of 2-acetoxyethylcyclohexanone (IVb).

The preparation of 2-hydroxyethylcyclohexanone (IVa) is already described,[6] but without mention of details and physical constants. We succeeded in the preparation of its acetate IVb by the following procedure.

Ethyl cyclohexanone-2-acetate (I) was obtained from cyclohexanone-pyrrolidine enamine and ethyl monobromoacetate by the method of Stork, *et al.*[7]; details of this preparation, not described so far, can be found in the Experimental part of this paper. Treatment of the keto-ester I with ethylene glycol yielded the ethylene ketal II. Both compounds I and II gave, as expected, the same 2,4-dinitrophenylhydrazone. The infrared spectrum of II showed presence of ketal[8] and ester bands, but absence of keto-carbonyl band. The ethylene-ketal II could be reduced either by lithium aluminum hydride in ether or, with similar yields, with sodium in ethanol to the ethylene ketal of 2-hydroxyethylcyclohexanone (IIIa). This compound gave a 2,4-dinitrophenylhydrazone corresponding to the derivative of 2-hydroxyethylcyclohexanone, and its infrared spectrum had the characteristic hydroxyl and ketal bands, but no carbonyl band. Direct acid hydrolysis[9] of the hydroxy-ketal IIIa failed to yield the expected ketoalcohol IVa and only mixtures of unsaturated cyclization compounds were obtained. This was avoided by first acetylating the hydroxy-ketal IIIa to the ketal-acetate IIIb, following with a mild hydrolysis to 2-acetoxyethylcyclohexanone IVb. The latter compound gave a 2,4-dinitrophenylhydrazone identical with the one obtained from the ketal-acetate IIIb and showed an infrared spectrum with acetate and keto bands.

The desired cyclohexanone derivative IVb thus obtained was smoothly oxidized by peracetic acid to the 1→6-lactone of 6-hydroxy-8-acetoxyoctanoic acid (V).[10] Its infrared spectrum had a very wide band at 1735 cm.$^{-1}$ and an acetate band at 1250 cm.$^{-1}$; it did not yield any 2,4-dinitrophenylhydrazone and, upon quantitative saponification, used up two equivalents of sodium hydroxide.

Although exceptions are known,[11] in general, lactones treated with thiourea in a strong mineral acid with alkaline hydrolysis of the isothiuronium salt thus obtained, yield thiol-acids.[12] In fact from our acetoxy-ε-lactone V in this way we easily obtained 6,8-dithioloctanoic acid (VI), which, after oxidation, gave 6-thioctic acid (VII) (19% over-all yield from cyclohexanone), with the same infrared spectrum of a sample of 6-thioctic acid synthesized by the method of Reed, *et al.*[13] The two samples, as well as their respective S-benzylisothiuronium salts,[14] did not give any melting point depression on admixture.

Acknowledgments.—The authors are indebted to Professor L. Ruzicka, Zurich, for the infrared spectra, to Professor G. Büchi, Cambridge, Mass., for a stimulating discussion and to the late Professor E. A. Braude, London, for the permission of reading his manuscript prior to publication.

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(1) For references, see H. Grisebach, *Angew. Chem.*, **68**, 554 (1956); G. W. E. Plaut and J. J. Bethiel, *Ann. Rev. Biochem.*, **25**, 485 (1956); L. Fontanella, *Il Farmaco, ed. sci.*, **10**, 274 (1955).

(2) See, for example, P. Boni, F. Reduzzi, G. Bile and V. Galloro, *Clin. Terap.*, **9**, 129 (1955); F. Rausch, *Klin. Wschr.*, **34**, 737 (1956); F. Steigman and S. M. Canahuati, *Fed. Proc.*, **15**, 487 (1956).

(3) L. Donatelli, "Atti del Simposio Internazionale sull'Acido Tioctico," Università di Napoli, 1955, pp. 45–145.

(4) D. S. Acker, U. S. Patent 2,752,373 (June 26, 1956); D. S. Acker and C. W. Todd, U. S. Patent 2,752,374 (June 26, 1956); E. A. Braude, R. P. Linstead and K. R. H. Wooldridge, *J. Chem. Soc.*, 3074 (1956); M. W. Bullock and J. J. Hand, Abstracts of Papers, 127th Meeting of the A.C.S., Cincinnati, Ohio, March, 1955, p. 8N-9N; K. Makino and M. Koike, *Enzymologia*, **16**, 215 (1953); I. Nakano and M. Sano, *J. Soc. Pharm. Japan*, **25**, 1296 (1955).

(5) For a review of the mechanism of ketone oxidation by peracid, see V. Franzen and H. Krauch, *Chem. Ztg.*, **79**, 627, 845 (1955).

(6) W. Prichard, U. S. Patent 2,459,520 (April 17, 1951).

(7) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).

(8) E. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 161 (1952).

(9) H. Schinz and G. Schäppi, *Helv. Chim. Acta*, **30**, 1493 (1947).

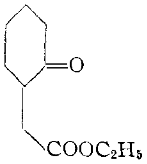
(10) E. A. Braude, *et al.*,[4] mention briefly in a footnote, as a byproduct of their 6-thioctic acid synthesis, a compound having the same formula.

(11) A. Campbell, *J. Chem. Soc.*, 4218 (1955).

(12) *E.g.*, L. Schotte, *Arkiv Kemi*, **8**, 457 (1956).

(13) L. J. Reed and Ching-I Niu, THIS JOURNAL, **77**, 416 (1955).

(14) I. C. Gunsalus, L. S. Barton and W. Gruber, *ibid.*, **78**, 1763 (1956).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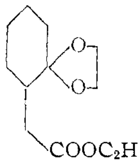
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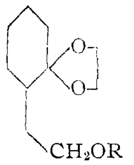
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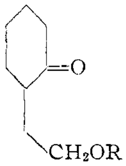
IIIb, R = OC—CH$_3$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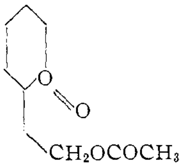
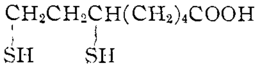

V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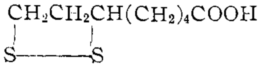
VI


$\underset{S—}{CH_2}CH_2\underset{—S}{CH}(CH_2)_4COOH$
VII

Experimental[15]

Ethyl Cyclohexanone-2-acetate (I).—In a round-bottomed flask fitted with a water separator, 29 g. of cyclohexanone, 85 g. of pyrrolidine and 200 ml. of dry benzene were refluxed for 1.5 hours. At this time the theoretical amount of water (6 ml.) had been separated and no more was evolved on longer heating. The solution was concentrated *in vacuo* to the oily residue of cyclohexanone-pyrrolidine enamine, so as to evaporate all the pyrrolidine in excess.

Thirty-seven and one-half grams of freshly distilled ethyl monobromoacetate was added dropwise to the boiling solution of the crude enamine in 150 ml. of dry benzene. Refluxing was then continued for another hour, the solvent and excess bromoester removed *in vacuo*, the thick residue refluxed for two hours, after addition of 100 ml. of methanol and 20 ml. of water. The solution was then concentrated at reduced pressure; the residue was treated with water and extracted with ether; the organic solution was washed successively with 2 *N* hydrochloric acid, sodium bicarbonate and water, dried over sodium sulfate and evaporated. The residue was fractionated twice *in vacuo* yielding 38.6 g. (71%),[16] b.p. 131–134° (13 mm.), n^{23}D 1.4564; infrared spectrum bands at 1715 (keto-carbonyl), 1735 (ester-carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.43; H, 8.93.

2,4-Dinitrophenylhydrazone, m.p. 126°. *Anal.* Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.88; H, 5.55; N, 15.54.

Ethylene Ketal of Ethyl Cyclohexanone-2-acetate (II).—A solution of 38.5 g. of ethyl cyclohexanone-2-acetate (I), 14.5 g. of ethylene glycol and 50 mg. of *p*-toluenesulfonic acid in 100 ml. of dry toluene was refluxed in a round bottomed flask fitted with a water separator. After three hours, 4.5 ml. of water had been collected. The cooled toluene solution was washed with aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated. The residue was distilled twice at reduced pressure yielding 42 g. (88%), b.p. 145–147° (13 mm.), n^{23}D 1.4630; infrared spectrum: bands at 1070 (ketal), 1735 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.02; H, 8.72.

Upon addition of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of the ketoester I, m.p. 126°, was obtained. The mixture of the two samples did not give any melting point depression.

Ethylene Ketal of 2-Hydroxyethylcyclohexanone (IIIa). a. **By Lithium Aluminum Hydride Reduction**.—A solution of 32 g. of ethylene ketal (II) in dry ether was added dropwise to a slurry of 4 g. of lithium aluminum hydride in 350 ml. of dry ether. The addition was completed after two hours and the mixture was refluxed for one hour longer. The excess reagent was destroyed with ethyl acetate and 2 *N* hydrochloric acid added. The organic layer, washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, was evaporated. The residue was fractionated twice at reduced pressure yielding 25 g. (96%), b.p. 148–150° (13 mm.), n^{23}D 1.4822; infrared spectrum bands at 1080 (ketal) and 3400 (hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.59; H, 9.90.

Addition of 2,4-dinitrophenylhydrazine yielded the expected 2,4-dinitrophenylhydrazone of 2-hydroxyethylcyclohexanone, m.p. 145–146.5°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.01; H, 5.83; N, 17.37.

b. **By Sodium–Ethanol Reduction**.—To a boiling, well-stirred solution of 5 g. of ketal ester II in 25 ml. of absolute ethanol were added simultaneously 5 g. of sodium and 30 ml. of absolute ethanol over a period of a half-hour. Boiling was continued for two hours. After cooling and evaporating the solution almost to dryness, the residue was poured in ice-water and extracted with ether. The organic layer was washed to neutrality with water, dried over sodium sulfate and evaporated. The residue was distilled twice, yielding 3.7 g. (90%), b.p. 148–150° (13 mm.), identical with the product obtained by lithium aluminum hydride reduction, with the same constants and the same 2,4-dinitrophenylhydrazone.

Ethylene Ketal at 2-Acetoxyethylcyclohexanone (IIIb).—Two grams of hydroxy-ketal IIIa dissolved in 6 ml. of pyridine was acetylated with 2 ml. of acetic anhydride at room temperature for two hours. The solution was poured in iced water and extracted with ether. The organic layer was washed successively with 2 *N* hydrochloric acid, aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated to an oil, which, distilled twice at reduced pressure, yielded 2.1 g. (91%), b.p. 152° (13 mm.), n^{27}D 1.4632; infrared spectrum 1090 (ketal), 1250 (acetate), 1740 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.15; H, 9.13.

Upon addition of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of the acetoxy-ketone IVb, m.p. 109–111°, was obtained.

2-Acetoxyethylcyclohexanone (IVb).—A solution of 2 g. of ethylene ketal of 2-acetoxyethylcyclohexanone (IIIb) and 75 mg. of *p*-toluenesulfonic acid in 20 ml. acetone was refluxed for one hour. The solvent was removed *in vacuo*, keeping the bath temperature below 40°; the oily residue was dissolved in ether, washed with aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated. After two distillations at reduced pressure 1.55 g. (90%) was obtained, b.p. 142–146° (15 mm.), n^{27}D 1.4565; infrared spectrum bands at 1250 (acetate), 1715 (keto-carbonyl), 1740 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.04; H, 8.82.

2,4-Dinitrophenylhydrazone, m.p. 109–111°. *Anal*. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.79; H, 5.46; N, 15.28.

1→6-Lactone of 6-Hydroxy-8-acetoxyoctanoic Acid (V).—A solution of 4.7 g. of 2-acetoxyethylcyclohexanone (IVb) in 16.3 ml. of peracetic acid[17] (containing 28.0 mg. of active oxygen per ml.) was allowed to stand at room temperature for 24 hours; chloroform was added and the resulting solution was washed to neutrality with aqueous sodium bicarbonate. The organic layer, washed with water, dried over sodium sulfate, was evaporated and the residue distilled twice at reduced pressure; yield 3.3 g. (65%), b.p. 126–130° (0.5 mm.), n^{23}D 1.4595, infrared spectrum bands at 1250 (acetate) and 1724–1750 (acetate and lactone) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; mol. wt., 200.21. Found: C, 60.36; H, 8.21; equiv. wt., 105.0.

6,8-Dithioloctanoic Acid (VI).—A mixture of 2.2 g. of acetoxylactone V, 6.5 g. of thiourea and 8.66 g. of 57% hy-

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(15) Melting points are uncorrected and determined in evacuated capillaries. Microanalyses and ultraviolet spectra from our Analytical Department (Drs. C. Ciriello and A. Costa).

(16) A. Dornow and E. Fleischmann, *Chem. Ber.*, **88**, 1340 (1955), obtained the same compound by another method starting from cyclohexanone with a yield of 48.8%.

(17) R. Criegee in "Methoden der organischen Chemie" (Houben-Weil), Band VIII, Sauerstoffverbindungen III, p. 41, Georg Thieme Verlag, Stuttgart, 1952.

driodic acid was refluxed for 36 hours and then hydrolyzed by adding 35 ml. of 30% aqueous potassium hydroxide and refluxing for 12 hours in the dark under nitrogen. The reaction mixture was extracted with ether, the aqueous layer separated, acidified with 2 *N* hydrochloric acid and extracted with chloroform. The chloroform solution, after washing to neutrality with water and drying over sodium sulfate, was concentrated and distilled *in vacuo* yielding 1.84 g. (80%) of 6,8-dithioloctanoic acid (VI), b.p. 180° (bath temperature) (1.5 mm.), $n^{22}\mathrm{D}$ 1.5225; infrared spectrum 1285, 1235 (OH-carboxyl), 1710 (CO-carboxyl) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74. Found: C, 46.37; H, 7.74.

6-Thioctic Acid (DL-α-Lipoic Acid) (VII).—1.01 g. of dithiol-acid (VI) were dissolved in 2.3 ml. of 2 *N* sodium hydroxide, diluted with 17 ml. of water containing 3.5 mg. of iron trichloride hexahydrate, yielding a dark red solution, through which a slow stream of oxygen was bubbled for 10 hours. The resulting pale yellow solution was washed with chloroform. The aqueous layer, acidified with 2 *N* hydrochloric acid, was extracted with chloroform and this was washed to neutrality and evaporated to dryness. The yellow oily residue crystallized upon trituration with petroleum ether (boiling range 40–60°). After one crystallization from petroleum ether, 0.8 g. of pure 6-thioctic acid (DL-α-lipoic acid) (VII) (80%) was obtained, m.p. 61–62°; ultraviolet spectrum $\lambda_{\max}^{\mathrm{EtOH}}$ 333 mμ (ε 147); infrared spectrum bands at 1285, 1235 (OH-carboxyl), 1700 (CO-carboxyl) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.68; S, 31.13. Found: C, 46.66; H, 6.90; S, 31.20.

S-Benzylisothiuronium salt, m.p. 153–154°[18] (from absolute methanol). *Anal.* Calcd. for $C_{16}H_{24}N_2O_2S_3$: C, 51.61; H, 6.45; N, 7.53; S, 25.79. Found: C, 51.53; H, 6.73; N, 7.56; S, 25.99.

NAPOLI, ITALY

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[18] M.p. 132–134°[14] has been observed once. This discrepancy may be due to crystallization and drying conditions.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Many-membered Carbon Rings. XIV. Transannular Ring Cleavage of Certain Cycloalkane Derivatives[1]

BY A. T. BLOMQUIST AND PETER R. TAUSSIG[2]

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Pyrolysis of cyclononyl acetate at 500° affords mainly 1,8-nonadiene (70%) together with *cis*-cyclononene (27%) and *trans*-cyclononene (1.5%). Thermal decomposition of cyclononyl S-methyl xanthate at various temperatures indicates that formation of 1,8-nonadiene occurs only at temperatures above 400°. Pure *trans*-cyclononene rearranges at 500° to 1,8-nonadiene (85%) and *cis*-cyclononene (15%) while pure *cis*-cyclononene, at 500°, yields only *ca.* 20% 1,8-nonadiene and 80% unchanged *cis*-cyclononene. Conformational analysis suggests two possible paths for the formation of the diene from cyclononyl acetate.

The discovery in recent years of transannular reactions[3,4] has done much to stimulate research in the chemistry of medium size rings. This has included several studies concerned with the course of elimination reactions of various derivatives of the cycloalkanes such as their amines, halides, acetates and xanthates.[5–7] This article presents studies of the thermal decomposition of the acetate and S-methyl xanthate of cyclononanol. In an earlier study of the pyrolysis of cyclodecyl acetate and cyclodecyl xanthate,[6] it was observed that a mixture of *cis*- and *trans*-cyclodecenes was produced rather than exclusively one stereoisomer as might have been expected. Further, it was noted that pyrolysis of cyclodecyl acetate gave, as a minor product, a low boiling "dienoid" substance. The latter was not fully characterized at that time.

Pyrolysis of cyclononyl acetate[8] at 500 ± 10° under the same conditions employed in the thermal decomposition of cyclodecyl acetate[6] afforded a pyrolyzate (78%) which interestingly contained only 30% of the expected mixture of *cis*- and *trans*-cyclononenes (IIa and IIb). The principal constituent (70%) of the pyrolyzate was found to be a low boiling compound analogous to the minor product formed in the thermal degradation of cyclodecyl acetate. This low boiling substance was readily identified as 1,8-nonadiene (I).

The structure of this hydrocarbon I was established as indicated below. Its properties agreed with those reported for 1,8-nonadiene by van Pelt[9] and by Everett.[10] Elementary analysis of I was in accord with the composition C_9H_{16} and quantitative catalytic hydrogenation of I indicated the presence of two double bonds. On oxidative ozonolysis I gave an acid (18%) which did not depress the melting point of an authentic sample of pimelic acid. Finally, the infrared absorption spectrum of I showed maxima at 10.07 and 10.97 μ, characteristic of a vinyl group, and was identical with the spectrum of 1,8-nonadiene obtained by pyrolysis of 1,9-nonanediol diacetate.

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[1] (a) For the preceding paper in this series see A. T. Blomquist and P. R. Taussig, THIS JOURNAL, **77**, 6399 (1955). (b) Presented before the Division of Organic Chemistry at the National Meeting of the American Chemical Society at Miami, Florida, April 7–12, 1957.

[2] Du Pont Post-Graduate Teaching Fellow. The work reported here was abstracted from part of the dissertation presented by Peter R. Taussig in September, 1956, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); V. Prelog, K. Schenker and W. Küng, *ibid.*, **36**, 471 (1953); V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würch, *ibid.*, **38**, 1095 (1955); V. Prelog and V. Boarland, *ibid.*, **38**, 1776 (1955).

[4] A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).

[5] A. T. Blomquist, R. E. Burge and A. C. Sucsy, *ibid.*, **74**, 3636 (1952).

[6] A. T. Blomquist and A. Goldstein, *ibid.*, **77**, 1001 (1955).

[7] A. C. Cope, R. A. Pike and C. F. Spencer, *ibid.*, **75**, 3212 (1953); A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955)

[8] M. Kobelt, D. Barman, V. Prelog and L. Ruzicka, *Helv. Chim. Acta*, **32**, 256 (1949).

[9] A. J. van Pelt, Jr., and J. P. Wibaut, *Rec. trav. chim.*, **60**, 55 (1941).

[10] J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950).