The first 50 ml. of eluate furnished 0.078 g. of yellow crystals, m.p. 50–52°. Evaporative sublimation at 50° (0.05 mm.) gave pure 2,2';4',2''-terthienyl, m.p. 53–54°.

Anal. Calcd. for $C_{12}H_8S_3$: C, 58.03; H, 3.25; S, 38.73. Found: C, 58.20; H, 3.27; S, 38.64.

A mixed m.p. with a sample of VIII prepared as described below was undepressed.

Methyl 2-Thienylacrylate.—2-Thienylacrylic acid[20] (61.7 g.) was converted to the methyl ester by refluxing for 4.5 hours with 150 ml. of absolute methanol and 33 g. of concentrated sulfuric acid. The ester, 54.3 g., melted at 48–49° after one crystallization from aqueous methanol.

Anal. Calcd. for $C_8H_8O_2S$: S, 19.06. Found: S, 19.10.

2-Thienyl-4-ketotetrahydrothiophene (VIII).—A mixture of 25.2 g. (0.15 mole) of methyl 2-thienylacrylate, 25.0 g. (0.20 mole) of ethyl mercaptoacetate and 1–2 ml. of piperidine was heated at 80–90° for 6 hours, then allowed to stand overnight. Distillation of the reaction mixture furnished 35.6 g. (82%) of mixed diester, b.p. 168–170 (0.6 mm.), n_D^{23} 1.5300. When 53.90 g. of diester sulfide was cyclized in the same manner as described for the preparation of II using 30.0 g. of sodium methoxide in 500 ml. of absolute ether, 17.0 g. (36%) of mixed cyclic ketoesters, b.p. 165–172° (1.0 mm.), was isolated. Decarboalkoxylation of 19.6 g. of ketoester by heating and stirring at 100° in the presence of 200 ml. of 15% sulfuric acid for 4.5 hours furnished 12.85 g. (61%) of 2-thienyl-4-ketotetrahydrothiophene, m.p. 59–60°, after recrystallization from petroleum ether (b.p. 90–100°) followed by ethyl alcohol.

Anal. Calcd. for $C_8H_8S_2O$: C, 52.14; H, 4.38; S, 34.80. Found: C, 52.43; H, 4.66; S, 34.62.

The Grignard Reaction with VIII.—To a Grignard reagent prepared from 4.45 g. of 2-bromothiophene, 1.0 g. of magnesium turnings and 40 ml. of anhydrous ether was added 5.00 g. of 2-thienyl-4-ketotetrahydrothiophene in 30 ml. of ether at such a rate that rapid refluxing was maintained. After decomposition of the complex with dilute sulfuric acid in the usual manner, the organic residue was heated briefly with 10 ml. of 20% sulfuric acid in order to complete the dehydration of the carbinol. The remaining oil (2.85 g.) was heated under reflux for 20 minutes with 3.4 g. of chloranil in 15 ml. of ethylene glycol. The reaction mixture was diluted with 100 ml. of 5% sodium hydroxide solution and extracted with benzene. The benzene extracts were washed with dilute hydrochloric acid and water. Removal of the solvent furnished 1.30 g. (20% from II) of 2,2';4',2''-terthienyl, m.p. 53–54°, after several recrystallizations from petroleum ether. A mixed m.p. with the terthienyl obtained by pyrolysis was undepressed.

GRINNELL, IOWA

(20) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

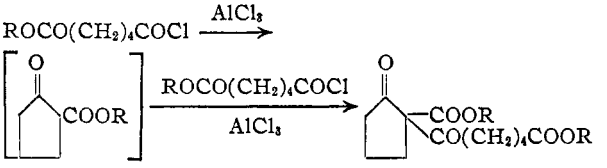
Synthesis of Thioctic Acid and 8-Methylthioctic Acid

BY MILON W. BULLOCK, JOHN J. HAND AND E. L. R. STOKSTAD

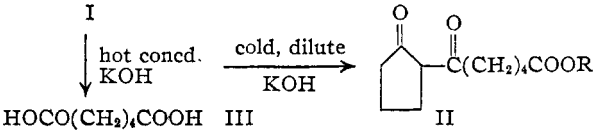
RECEIVED SEPTEMBER 20, 1956

Improved methods are described for the preparation of thioctic acid, 8-methylthioctic acid and intermediates. The condensation of methyl and ethyl 5-chloroformylvalerate with ethylene, propylene and isobutylene have been improved to yield easily purified unsaturated ketoesters. The addition of thioacetic acid to the unsaturated ketones is described as is the reduction of the addition products to the corresponding alcohol.

Several methods for the preparation of thioctic acid have been described.[1–6] Some of the more useful methods require as an intermediate the condensation product of ethyl 5-chloroformylvalerate and ethylene. The initial condensation product, ethyl 8-chloro-6-oxoöctanoate has been dehydrohalogenated thermally to yield the desired ethyl 6-oxo-7-octenoate.[1] We have found that the yields in the condensation and dehydrohalogenation reaction are greatly improved if the condensation is done in ethylene chloride and the intermediate β-chloroketone dehydrohalogenated with sodium acetate. Vigorous stirring is essential during the addition of ethylene. The stirrer should be of the propeller type and should be turning at a sufficiently high speed so that the ethylene is suspended in the reaction mixture as fine bubbles. A side reaction occurring to the extent of 10–15% when ethylene is employed as the olefin is the self condensation of the acid chloride to form ultimately the cyclopentanone derivative I.



The structure of the by-product I has been partially confirmed by the degradation reactions



The degradation product II was obtained from partial saponification of the methyl ester with cold potassium hydroxide. It was isolated as the di-2,4-dinitrophenylhydrazone. Product II was also obtained by redistillation of an old sample of I which had been stored with a trace of hydrogen chloride. The ester gave a pale orange color with ferric chloride solution. Strong hydrolysis of the ethyl ester I with methanolic potassium hydroxide gave 69% yield of adipic acid (III). No readily purified products were obtained by acid hydrolysis.

When propylene or isobutylene was substituted

(1) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce, M. H. von Saltza, F. Sanders and E. L. R. Stokstad, THIS JOURNAL, **76**, 1828 (1954).

(2) Q. F. Soper, W. E. Buting, J. W. Cochran, Jr., and A. Pohland, *ibid.*, **76**, 4109 (1954).

(3) L. J. Reed and Ching-I Niu, *ibid.*, **77**, 416 (1955).

(4) A. F. Wagner, E. Walton, C. H. Hoffman, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5140 (1955).

(5) E. Walton, A. F. Wagner, F. A. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5144 (1955).

(6) E. A. Braude, R. P. Linstead and K. H. R. Wooldridge, *Chemistry & Industry*, 508 (1955).

for the ethylene the principal side reaction became the self condensation of the olefin to form products which have not been identified.

The unsaturated ketoesters obtained from the condensation reaction added thioacetic acid to yield the corresponding ω-acetylthioketoesters in high yield. The ease of addition of the thioacetic acid decreased with increasing substitution on the carbon atom beta to the carbonyl group. The addition products were stable and could be purified by distillation at reduced pressure.

The ethyl 8-acetylthio-6-oxoöctanoate and ethyl 8-acetylthio-6-oxononanoate are reduced smoothly to the corresponding hydroxy compounds with sodium borohydride. Ethyl 8-acetylthio-6-oxononanoate also was reduced with aluminum isopropylate in isopropyl alcohol. Neither reducing agent gave a stereospecific reduction as evidenced by the composition of the 8-methylthioctic acid obtained as the end product of the syntheses. The product obtained with isobutylene, ethyl 8-acetylthio-8-methyl-6-oxononanoate, yielded only an impure product having a low sulfur content on treatment with sodium borohydride.

Saponification of the reduced products yielded the 6-hydroxy-8-mercaptoöctanoic acid and 6-hydroxy-8-mercaptononanoic acid. Neither of the acids could be purified by distillation but could be converted directly to the corresponding dithiol acids by known procedures.[1] The 8-methyl-6-hydroxy-8-mercaptoöctanoic acid did not yield two readily separable isomeric 8-methylthioctic acids. The product, which was obtained in satisfactory yield, is believed to be a molecular compound containing both pairs of diastereoisomers. This conclusion is based on the improbability that both the aluminum isopropylate and the sodium borohydride reduction would be entirely stereospecific, and the fact that bioautographs of paper chromatograms of this material showed both zones of inhibition and zones of growth. Apparently, one diastereoisomer stimulates growth and the other functions as an inhibitor.[7]

Acknowledgment.—The authors are indebted to Mr. W. Fulmor for the infrared analyses, to Mr. L. Brancone and staff for the microanalyses, and to Dr. E. L. Patterson and Mr. M. H. von Saltza for assistance with the paper chromatograms and bioautographs.

Experimental

Methyl 5-Chloroformylvalerate.—Monomethyl adipate (500 g., 3.11 moles) and 393 g. (3.3 moles) of thionyl chloride were warmed slowly to about 50° and 200 ml. of carbon tetrachloride was added. The solution was refluxed one hour and the solvent and excess thionyl chloride distilled under the reduced pressure of an aspirator. Distillation of the product gave 382 g. (2.14 moles), 69% of pure product b.p. 122° at 10 mm., $n^{20}D$ 1.4465 and d^{20} 1.145.

Anal. Calcd. for $C_7H_{11}O_3Cl$: Cl, 19.84. Found: Cl, 19.73.

A more successful procedure was to add a 10% excess of thionyl chloride to the half-ester and allow the mixture to stand overnight. The flask is then warmed gently to drive out most of the dissolved gases and the product distilled. The yield by this method was 95%.

(7) The general procedures for making the paper chromatograms and bioautographs are given by E. L. Patterson, J. V. Pierce, E. L. R. Stokstad, C. E. Hoffman, J. A. Brockman, Jr., F. P. Day, M. E. Macci and T. H. Jukes, THIS JOURNAL, **76**, 1823 (1954).

Methyl 6-Oxo-7-octenoate.—In a flask equipped with an efficient stirrer, were placed 572 g. (4.27 moles) of anhydrous granular aluminum chloride and 800 ml. of ethylene chloride. The flask was submerged in an ice-bath while 382 g. (2.14 moles) of methyl 5-chloroformylvalerate was added at such a rate that the temperature remained between 35–40°. Ethylene was then passed into the rapidly stirred solution. Absorption of the olefin was rapid. The temperature was maintained at 40–45° by cooling with an ice-bath at first and by warming later. After one hour the absorption of ethylene was complete. The contents of the reaction flask were stirred into a mixture of a liter of ethyl acetate and ice to which approximately 0.5 g. of hydroquinone had been added. The organic layer was separated and washed once with water and once with 2 liters of ice-cold *N* sodium hydroxide. A further 0.5 g. of hydroquinone was added and the organic solution was dried over magnesium sulfate. The drying agent was filtered and the solution was then stirred at reflux temperature three hours with 352 g. (4.27 moles) of anhydrous sodium acetate (the two-phase system often foams a great deal); the reaction mixture was extracted twice with two-liter volumes of ice-water and dried over sodium sulfate. The solvent was distilled off at the water-pump and the product purified by distillation through a 24″ electrically heated Vigreux column, b.p. 97–99° at 0.35 mm. (117° at 9 mm.), $n^{20}D$ 1.4519 and d^{20} 1.016. The yield was 255.5 g. (1.5 moles), 70%.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 63.13; H, 8.30.

In addition to the desired product there was obtained 41.6 g. of colorless liquid b.p. 135–136° at 0.25 mm. This product was not analyzed but the analysis of the analogous compound from the reaction of ethyl 5-chloroformylvalerate with ethylene indicates the empirical formula to be $C_{14}H_{20}O_6$. The compound is believed to be methyl 6-oxo-6-(1-carbomethoxy-2-oxocyclopentyl)-hexanoate. A sample of this material was partially hydrolyzed by storing overnight with an excess of methanolic potassium hydroxide. This preparation gave little or no adipic acid, but a neutral fraction gave a low yield of a di-2,4-dinitrophenylhydrazone which had the correct empirical formula for the expected degradation product methyl 6-oxo-6-(2-oxocyclopentyl)-hexanoate di-2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{24}H_{26}N_8O_{10}$: C, 49.48; H, 4.47; N, 19.11. Found: C, 49.16; H, 5.13; N, 18.45.

Redistillation of a sample of crude material containing traces of hydrogen chloride, which had been stored for about a year, gave a pure product, b.p. 97–98° at 0.05 mm., n_D^{20} 1.4531 and d^{20} 1.081. This product gave a pale orange color with ferric chloride. This product appears to be methyl 6-oxo-6-(2-oxocyclopentyl)-hexanoate.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.82; H, 8.51.

Ethyl 6-Oxo-7-octenoate, Ethyl 6-Oxo-6-(1-carbethoxy-2-oxocyclopentyl)-hexanoate and Degradation Products.—Ethyl 6-oxo-7-octenoate was prepared in 70.6% yield in the same way as the methyl ester described above. The physical constants are in an earlier publication.[1] From a 1.04-mole run there was obtained 23.4 g. of higher boiling material distilling 122° at 0.07 mm., $n^{27.5}D$ 1.4460. This product, which gave no color with ferric chloride, has been identified as ethyl 6-oxo-6-(1-carbethoxy-2-oxocyclopentyl)-hexanoate.

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 61.12; H, 8.34; sapn. equiv., 157. Found: C, 61.47; H, 8.62; sapn. equiv., 157.

Forty-seven grams (0.149 mole) of the by-product was poured into a solution of 20 g. of potassium hydroxide in 100 ml. of 75% ethanol. The reaction was sufficiently exothermic so that the basic solution refluxed spontaneously. A precipitate of potassium adipate formed on standing overnight. The salt was collected and converted to adipic acid. The m.p. and mixed m.p. with adipic acid was 151°. Additional adipic acid was recovered from the filtrate bringing the total yield of adipic acid to 15 g. (0.103 mole). In addition to the adipic acid there was obtained 11 g. of products distilling 114–118° at 0.1 mm. No pure product could be obtained from this fraction.

Methyl 8-Acetylthio-6-oxoöctanoate.—Methyl 6-oxo-7-octenoate, 182 g. (1.07 moles), was treated with swirling and cooling with 93.5 g. (1.23 moles) of thioacetic acid, added in small portions through the condenser. The reaction mix-

ture was left standing two hours and the product vacuum distilled, b.p. 138–140° at 0.1 mm. The yield was 250 g. (1.01 moles), 94.6%. The material had $n^{28.5}$D 1.4810 before it crystallized to a white solid having m.p. 37°.

Anal. Calcd. for $C_{11}H_{18}O_4S$: C, 53.63; H, 7.36; S, 13.00. Found: C, 53.93; H, 7.68; S, 13.12.

6-Thioctic Acid and 2-(δ-Carboxybutyl)-trimethylene Sulfide.—A solution of 15 g. (0.376 mole) of sodium hydroxide in 150 ml. of water was added to 27 g. (0.103 mole) of ethyl 8-acetylthio-6-hydroxyoctanoate.[1] The solution became homogeneous when shaken. The solution was refluxed 35 minutes, cooled and acidified with concentrated hydrochloric acid. The product was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled leaving a residue weighing 26 g. and having the odor of acetic acid. To this crude 6-hydroxy-8-mercaptoöctanoic acid were added 75 g. of thiourea and 200 ml. of 50% hydriodic acid. The resulting solution was heated at reflux ten hours and cooled. The solution was made alkaline by the addition of a solution of 50 g. of sodium hydroxide in 150 ml. of water and refluxed 30 minutes. The solution was cooled and acidified with hydrochloric acid. The product was extracted with three 80-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and distilled leaving 21.5 g. of oil. The crude product was distilled and the products collected in two fractions. The fraction distilling 136–150° at 0.15 mm. amounted to 3.6 g. This material was primarily 2-(δ-carboxybutyl)-trimethylene sulfide. This material was redistilled and the fraction distilling 129–130° at 0.1 mm. collected as product. This product was not pure. It was identified as the barium salt, monohydrate, m.p. 258–260°, and as the S-benzylthiuronium salt, m.p. 152°. Both salts were recrystallized from 95% ethanol.

Anal. Calcd. for $C_{16}H_{28}O_5S_2Ba$: C, 38.29; H, 5.62; S, 12.78; Ba, 27.37. Found: C, 38.24; H, 5.86; S, 13.09; Ba, 27.44. Calcd. for $C_{16}H_{24}O_2S_2N_2$: C, 56.43; H, 7.10; S, 18.83. Found: C, 55.89; H, 7.33; S, 18.38.

The second fraction distilling 150–168° at 0.15 mm. and weighing 10.5 g. was crude 6,8-dimercaptoöctanoic acid. It was converted to thioctic acid by the procedure described in reference 1. The yield of pure acid was 31%.

Methyl 6-Oxo-7-nonenoate.—Anhydrous granular aluminum chloride 907.2 g. (6.81 moles) and 2 liters of ethylene chloride were cooled in an ice-bath while 612 g. (3.43 moles) of methyl 5-chloroformylvalerate was added at such a rate that the temperature did not rise above 45°. Propylene was then passed into the rapidly stirred solution for 1.5 hours while the temperature was maintained 40–45° by cooling. The reaction mixture was poured slowly into a mixture of 1.5 liters of ethyl acetate containing 1 g. of hydroquinone and a large quantity of crushed ice. The organic layer was separated, washed with cold water, then with cold dilute sodium hydroxide solution, then dried over sodium sulfate and treated with 565 g. (6.87 moles) of anhydrous sodium acetate. The mixture was refluxed 2.25 hours. Water was added to dissolve the salts and the organic layer was separated. Distillation of the solvent left two phases. The products were partitioned between ligroin and methanol containing a small amount of water. The methanol layer was distilled and the residue purified by vacuum distillation. The fraction distilling 113–115° at 2 mm. was collected as product. The yield was 315.7 g. (1.71 moles), 49.8%. A small sample was redistilled to obtain an analytical sample. The pure material had b.p. 127° at 5.3 mm. and n^{20}D 1.4608.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.96.

Ethyl 6-Oxo-7-nonenoate.—The ethyl ester was prepared by the method previously described for the preparation of ethyl 6-oxo-7-octenoate.[1] The yield of material, b.p. 103–105° at 0.6–1 mm., n^{20}D 1.4578, was 51%. The analysis was poor due to the presence of a hydrocarbon co-distilling with the ester. The impurity was isolated in the next synthesis.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.67; H, 9.29.

Ethyl 8-Acetylthio-6-oxononanoate.—One hundred twenty-nine and three-tenths grams (0.69 mole) of ethyl 6-oxo-7-nonenoate was treated with 55 ml. (0.705 mole) of thioacetic acid added in portions with swirling. The temperature rose to approximately 100° and the mixture was then heated on the steam-bath one-half hour and the excess thioacetic acid distilled off under reduced pressure. The product was vacuum distilled through a 6″ vacuum jacketed Vigreux column. After a fairly large forerun, which was two phase, the remainder of the product distilled 140° at 0.05 mm. and had n^{20}D 1.4772 and d^{20} 1.071. An additional 13.5 g. of product was obtained by redistilling the lower phase of the forerun bringing the total yield of pure product to 141.4 g. (0.515 mole), 75%.

Anal. Calcd. for $C_{13}H_{22}O_4S$: C, 56.90; H, 8.08; S, 11.68. Found: C, 56.83; H, 7.76; S, 11.84.

From the upper phase of the forerun there was obtained 10.5 g. of oily material which was soluble in ligroin but insoluble in methanol. The product was washed with methanol, dissolved in ether and washed with a solution of Girard reagent T, washed with sodium hydroxide and distilled. This gave a colorless product, b.p. 90° at 0.05 mm., having n^{20}D 1.4585 and d^{20} 0.705. This product is believed to be a propylene polymer.

Anal. Found: C, 85.58; H, 14.28; mol. wt., 287 (Rast, camphor). $C_{21}H_{42}$ requires C, 85.63; H, 14.37; mol. wt., 294.5.

Reduction of Ethyl 8-Acetylthio-6-oxononanoate with Sodium Borohydride.—A solution of 52.5 g. (0.191 mole) of ethyl 8-acetylthio-6-oxononanoate in 150 ml. of alcohol was treated with stirring with a solution of 3.8 g. (0.0955 mole as 95%) sodium borohydride over a period of 15 minutes. The temperature of the reaction mixture rose to about 70°. A test for excess reducing agent (acidified aliquot) was positive. The ethanol was distilled off on the steam-bath—first at atmospheric pressure and finally under reduced pressure. The residue was diluted with 200 ml. of ether and a solid filtered off. The ether solution was washed with water, with dilute sulfuric acid and dried over sodium sulfate containing a small amount of sodium bicarbonate. Distillation of the ether left 44 g. of a yellow oil which was purified by two distillations to yield 29 g. (0.105 mole, 55%) of product, b.p. 108–109° at 0.05 mm., n^{20}D 1.4678 and d^{20} 1.036.

Anal. Calcd. for $C_{13}H_{24}O_4S$: C, 56.49; H, 8.75; S, 11.60. Found: C, 56.14; H, 8.13; S, 11.44.

This product had an abnormally weak unbonded hydroxyl absorption at 2.85 μ indicating that some of the acetyl group may have migrated to the oxygen atom. This type of rearrangement has been discussed by Owen.[8]

Reduction of Ethyl 8-Acetylthio-6-oxononanoate with Aluminum Isopropylate.—A mixture of 40 g. (0.145 mole) of ethyl 8-acetylthio-6-oxononanoate and 200 ml. of dry isopropyl alcohol containing 37.4 g. (0.183 mole) of distilled aluminum isopropoxide was refluxed and acetone was taken off through an efficient column. After six hours an additional 20 g. (0.098 mole) of aluminum isopropoxide in 100 ml. of isopropyl alcohol was added. After an additional hour a test for acetone in the distillate showed that the reaction was nearing completion. After refluxing overnight only a very small amount of acetone could be obtained. After removal of most of the solvent the residue was shaken with 500 ml. of cold 3 *N* hydrochloric acid. The product was extracted with two 100-ml. portions of chloroform. The chloroform extracts were washed with dilute hydrochloric acid, half-saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the solvent left an oil which was purified by vacuum distillation. The product distilled 111–115° at 0.04 mm. The yield was 29.1 g. (0.1055 mole), 72.5%. The product from this reduction had n^{20}D 1.4714 and d^{20} 1.010. Although this preparation was not pure it was equivalent to the material produced by sodium borohydride for the preparation of 8-methylthioctic acid.

Anal. Calcd. for $C_{13}H_{24}O_4S$: C, 56.49; H, 8.75; S, 11.60. Found: C, 57.66; H, 9.51; S, 13.09.

8-Methylthioctic Acid (5-Methyl-1,2-dithiolane-3-valeric Acid.—Ethyl 8-acetylthio-6-hydroxynonanoate, 26.6 g. (0.0963 mole), was saponified by refluxing 40 minutes with a solution of 8.5 g. (0.212 mole) of sodium hydroxide in 100 ml. of water. The solution was cooled, acidified and extracted with two 100-ml. portions of ether. The combined

(8) L. N. Owen, *J. Chem. Soc.*, 817 (1952), and previous papers.

ether extracts were dried over sodium sulfate and distilled leaving 27 g. of a colorless viscous oil. This oil was treated with 75 g. of thiourea followed by 200 g. of 50% hydriodic acid and heated at reflux for 18 hours. The cooled solution was made alkaline with 5 *N* sodium hydroxide and refluxed 40 minutes, cooled and acidified with concentrated hydrochloric acid. The aqueous solution was extracted with two 100-ml. portions of chloroform. The chloroform extracts were dried over sodium sulfate and distilled. The yellow oily residue was distilled through a 6″ vacuum jacketed Vigreux column. The fractions distilling 148–166° at 0.1 mm. and weighing 9.4 g. were collected as product. The distillate partially crystallized on standing a short time. The crystals were collected and washed with a mixture of one part cyclohexane and two parts petroleum ether, b.p. 60–68°. This gave 4.0 g. of yellow crystals, m.p. 45–46°. The oil fraction was dissolved in sodium hydroxide solution and oxidized to the cyclic disulfide in the same manner as described for thioctic acid. This gave 2.0 g. of product, m.p. 52°. After recrystallization of this product from 50 ml. of petroleum ether, b.p. 60–68°, it had m.p. 54–54.5°. On storage the lower melting product changed to the higher melting form. A mixed m.p. showed no depression. The total yield of pure 8-methylthioctic acid was 5.6 g. (0.0254 mole), 26%.

Anal. Calcd. for $C_9H_{16}O_2S_2$: C, 49.06; H, 7.32; S, 29.10; neut. equiv., 220.4. Found: C, 49.02; H, 7.85; S, 29.47; neut. equiv., 224.

Bioautographs of paper chromatograms showed two zones of growth and two zones of inhibition. The double zones are due to air oxidation of the disulfides to the biologically equivalent thiosulfenates. The bioautographs were done by the method of Patterson, *et al.*[7]

Ethyl 8-Methyl-6-oxo-7-nonenoate.—A cooled mixture of 266.7 g. (2 moles) of anhydrous granular aluminum chloride and 400 ml. of nitrobenzene was treated with 193 g. (1 mole) of ethyl 5-chloroformylvalerate added with stirring over a period of five minutes. Isobutylene was then passed into the rapidly stirred solution for 1.5 hours. The mixture was allowed to warm to room temperature, and isobutylene was passed into the solution for an additional half hour. At no time did isobutylene condense in the Dry Ice condenser; however, the volume of the reaction flask increased considerably indicating that the excess isobutylene was polymerized by the catalyst. The reaction mixture was stirred into a mixture of 500 ml. of ethyl acetate and ice. The organic layer was separated, washed with dilute sodium hydroxide, dried over sodium sulfate, diluted with 500 ml. of ethyl acetate and stirred 2 hours at reflux temperature (82°) with 123 g. (1.5 moles) of powdered anhydrous sodium acetate. The mixture was cooled and the solid material filtered off. The filtrate was adjusted to *p*H 8 with 20% sodium hydroxide, washed twice with water and dried over sodium sulfate. The solvents were distilled off *in vacuo* and the product purified by vacuum distillation. The fraction distilling 127–140° at 2 mm. was collected as product. The yield was 126 g. (0.594 mole, 59%). An aliquot was redistilled to obtain an analytical sample. The best material had b.p. 120° at 1.2 mm. and $n^{21}D$ 1.4610.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 68.76; H, 9.84.

Ethyl 8-Acetylthio-8-methyl-6-oxononanoate.—Sixty-two grams (0.82 mole) of thioacetic acid was stirred into 115 g. (0.543 mole) of ethyl 8-methyl-6-oxo-7-nonenoate. The reaction mixture was warmed slowly to 105° and maintained at this temperature for 30 minutes. The product was purified by vacuum distillation. The fraction distilling 118–140° at 0.1–0.5 mm. was collected as product. The yield was 130 g. (0.452 mole), 83.5%. A sample was crystallized from ligroin at low temperature and redistilled to obtain an analytical sample. This material, b.p. 130° at 0.05 mm., had $n^{20}D$ 1.4770 and m.p. 3°.

Anal. Calcd. for $C_{14}H_{24}O_4S$: C, 58.30; H, 8.38; S, 11.11. Found: C, 58.75; H, 8.58; S, 10.71.

Attempts to reduce this product with sodium borohydride did not yield any pure product.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

Convenient Synthesis of Thioctic Acid

BY MILON W. BULLOCK, JOHN J. HAND AND E. L. R. STOKSTAD

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Suitable methods are described for the preparation of thioctic acid and 8-methylthioctic acid from readily available intermediates. The preparations involve a direct conversion of a carbonyl oxygen to a mercapto group by reducing in an atmosphere of hydrogen sulfide and hydrogen in the presence of a sulfactive catalyst.

In the course of our studies on thioctic acid and certain related compounds it became desirable to have a method for the economical and rapid preparation of relatively large amounts of these compounds. The methods developed earlier in these laboratories and others[1–7] serve well to prepare small amounts of thioctic acid and some related compounds. However, these methods are expensive to operate and the over-all yields are rather low.

Processes for preparing thioctic acid directly from ethyl 6-oxo-7-octenoate or 8-benzylthio-6-oxoöctanoic acid have been described by Soper, *et al.*,[2] but the conditions necessary for obtaining a satisfactory yield were not worked out. Additional examples of preparing thioctic acid by a direct reduction of a carbonyl group have been described by Acker[8] and Acker and Todd.[9] These methods have been extended and improved so that satisfactory yields of thioctic acid are conveniently obtained from readily available intermediates such as ethyl 6-oxo-7-octenoate or the 8-acetylthio or benzylthio derivatives.[1,7] The stoichiometry of the process is shown below.

There are undoubtedly other side reactions which take place also, but these listed below ap-

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(4) A. F. Wagner, E. Walton, C. H. Hoffman, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5140 (1955).

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(7) M. W. Bullock, J. J. Hand and E. L. R. Stokstad, THIS JOURNAL, **79**, 1975 (1957).

(8) D. S. Acker, U. S. Patent 2,752,373 (1956).

(9) D. S. Acker and C. W. Todd, U. S. Patent 2,752,374 (1956).