intervals in 60-ml. portions over that period. This was then diluted with water and extracted with ether. The solvent was removed under reduced pressure and the residual oil was extracted with hot aqueous sodium carbonate. The reduced acid III separated on acidification of the alkaline filtrate as oil which soon solidified. After crystallization from petroleum–ether (b.p. 40–60°), it afforded 7 g. (75%) of colorless needles, m.p. 114–115°. A mixed m.p. with the keto acid II was depressed.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.4; H, 9.2. Found: C, 78.52; H, 8.85.

1-Keto-1,2,3,4-tetrahydronaphthalene-2,2-spiro-(2′-*n*-propylcyclopentane (IV).—Five grams of the butyric acid (III) was heated on the steam-bath, with stirring, with a mixture of 15 ml. of sulfuric acid (sp. gr. 1.84) and 5 ml. of water for 1.5 hours. The dark brown reaction mixture was poured in a thin stream on crushed ice and the ketone extracted with ether. The ether solution was washed with aqueous ammonia and water and was dried (sodium sulfate). The neutral matter left after removal of ether, afforded, on distillation, 3.5 g. (78%) of the spiro-ketone IV as colorless oil having a characteristic sweet odor, b.p. 168–170° (6 mm.), $n^{30}D$ 1.5464.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.3; H, 9.1. Found: C, 84.12; H, 9.31.

The ketone did not form semicarbazone or 2,4-dinitrophenylhydrazone.

1,2,3,4-Tetrahydronaphthalene-2,2-spiro-(2′-*n*-propylcyclopentane) (I).—Three grams of the spiro-ketone IV was gently boiled under reflux with 15 g. of amalgamated zinc, covered with 15 ml. of concd. hydrochloric acid, 6 ml. of water, 9 ml. of toluene and 4.5 ml. of acetic acid for 48 hours, with addition of 10-ml. portions of concd. hydrochloric acid at 12-hour intervals. The reaction mixture was then cooled, diluted with water and extracted three times with 50-ml. fractions of ether. The ether solution was washed with water, dried and evaporated to a light brown oil which was separated into two fractions by distillation *in vacuo:* (a) b.p. 150–155° at 6 mm. (1.5 g.), (b) b.p. 165–172° at 6 mm. (1 g.). The first fraction on redistillation yielded 1.1 g. (40%) of the spiran as colorless oil, b.p. 150–152° (6 mm.), $n^{30}D$ 1.5358. The second fraction, on redistillation gave 0.8 g. of the unreduced spiro-ketone.

Anal. Calcd. for $C_{17}H_{24}$: C, 89.5; H, 10.5. Found: C, 88.92; H, 10.25.

Dehydrogenation of the Spirohydrocarbon (I) with Platinum-on-charcoal.—A mixture of 1.0 g. of the spirohydrocarbon (I) and 0.1 g. of 10% platinum-on-charcoal catalyst[14] was heated in a metal-bath in an atmosphere of carbon dioxide at 290–300° for 6 hours. The temperature was then raised to 330° in course of 6 hours when evolution of hydrogen ceased. The mass was cooled and extracted with 50 ml. of benzene. The extract, which exhibited violet fluorescence, was filtered and the light brown oil, left after removal of the solvent, was distilled over sodium under reduced pressure. The liquid distillate (0.5 g.) was warmed with an ethanolic solution of picric acid and the separated picrate after one crystallization from absolute ethanol was obtained as red needles, m.p. 227°.[15]

Anal. Calcd. for $C_{23}H_{15}N_3O_7$: C, 62.0; H, 3.4. Found: C, 61.9; H, 3.42.

The picrate was decomposed with aqueous ammonia and the liberated hydrocarbon was taken up in ether. The ether solution was washed with water. Removal of the solvent afforded 0.1 g. of the solid hydrocarbon which crystallized from methyl alcohol in colorless flakes, m.p. 147°.[15] The mixed m.p. of this sample with an authentic sample of pyrene was depressed.

Anal. Calcd. for $C_{17}H_{12}$: C, 94.44; H, 5.56. Found: C, 94.4; H, 5.6.

The *sym*-trinitrobenzene complex was prepared with the hydrocarbon in ethanolic solution. After crystallization from methanol–benzene mixture, it was obtained as orange needles, m.p. 246–247°.

Anal. Calcd. for $C_{23}H_{16}N_3O_6$: C, 64.3; H, 3.5. Found: C, 64.42; H, 3.47.

The hydrocarbon responded to the color reaction shown by Bachmann and Edgerton[15] in the case of 1-methylpyrene. It gave a golden yellow solution with concd. sulfuric acid having a green fluorescence. On gentle warming, the color became olive-green with intense violet fluorescence.

Acknowledgment.—The author expresses his indebtedness to Dr. S. C. Sengupta, Professor of Chemistry, Presidency College, Calcutta, for his valuable help and interest in this work. This investigation was aided by a grant sanctioned by the Government of West Bengal.

(14) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

(15) W. E. Bachmann and R. O. Edgerton, THIS JOURNAL, **62**, 2970 (1940), record m.p. of 1-methylpyrene as 147.5–148.5° and that of its picrate as 226–227°.

KRISHNAGAR, WEST BENGAL, INDIA

[CONTRIBUTION FROM THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Syntheses of DL-α-Lipoic Acid

BY LESTER J. REED AND CHING-I NIU

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Crystalline DL-α-lipoic acid has been obtained in good yield from ethyl 6,8-dibromoöctanoate and from the corresponding dichloro ester. The former ester was treated with potassium thiolacetate in boiling ethanol, followed by alkaline hydrolysis and oxidation of the resulting 6,8-dimercaptoöctanoic acid (dihydro-α-lipoic acid) with iodine or with oxygen in the presence of ferric ion. Both the dibromo and the dichloro esters were converted in high yield to 6,8-dibenzylmercaptoöctanoic acid by treatment with sodium benzylmercaptide in boiling ethanol, followed by alkaline hydrolysis. 6,8-Dibenzylmercaptooctanoic acid was reduced in high yield to 6,8-dimercaptoöctanoic acid with sodium in liquid ammonia. Ethyl 6,8-dibromooctanoate was produced by addition of anhydrous hydrogen bromide to ethyl 6-oxo-7-octenoate, followed by reduction with sodium borohydride to give ethyl 8-bromo-6-hydroxyoctanoate, which was converted to the dibromo ester with phosphorus tribromide. The dichloro ester was obtained by addition of ethyl δ-chloroformylvalerate to ethylene in the presence of aluminum chloride, followed by reduction with sodium borohydride to produce ethyl 8-chloro-6-hydroxyoctanoate, and treatment of the latter with thionyl chloride.

DL-α-Lipoic acid (6-thioctic acid) was obtained in low yield[1,2] by treating 4-(α-tetrahydrofuryl)-butyric acid with hydrogen bromide or potassium iodide–phosphoric acid to produce a mixture of halogen-substituted lactones of octanoic acid, which were converted to dimercaptoöctanoic acids by treatment with thiourea and acid. The dimercaptoöctanoic acids were oxidized to a mixture of

(1) C. S. Hornberger, Jr., R. F. Heitmiller, I. C. Gunsalus, G. H. F. Schnakenberg and L. J. Reed, THIS JOURNAL, **75**, 1273 (1953).

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

disulfides, which was purified extensively to obtain crystalline DL-α-lipoic acid.[1]

An improved synthesis[2] consisted of adding ethyl δ-chloroformylvalerate to ethylene in the presence of aluminum chloride to yield on distillation ethyl 6-oxo-7-octenoate. Thiolacetic acid was added to the vinyl ketone, followed by reduction with sodium borohydride to give ethyl 8-acetylmercapto-6-hydroxyoctanoate. Saponification of this ester and treatment with hydriodic acid and thiourea produced, after hydrolysis, crude 6,8-dimercaptoöctanoic acid, which was oxidized to the cyclic disulfide. The over-all yield of crystalline product, based on ethyl δ-chloroformylvalerate, was approximately 8%.

Other syntheses of DL-α-lipoic acid from ethyl 6-oxo-7-octenoate have been reported.[3] Benzyl mercaptan was added to the vinyl ketone, followed by hydrolysis and reduction with sodium borohydride to give 8-benzylmercapto-6-hydroxyoctanoic acid. Tosylation of the latter substance followed by replacement of the tosyloxy group by the benzylmercapto group yielded crude 6,8-dibenzylmercaptoöctanoic acid. This substance was reduced and the resulting 6,8-dimercaptoöctanoic acid was oxidized to DL-α-lipoic acid. Reduction of 8-benzylmercapto-6-oxoöctanoic acid by means of hydrogen and hydrogen sulfide in the presence of a cobalt sulfide catalyst, or of 6,6,8-tribenzylmercaptoöctanoic acid with sodium in liquid ammonia, followed in both cases by oxidation with iodine, also gave the desired product. The over-all yields of DL-α-lipoic acid by these procedures were somewhat lower than reported by Bullock and co-workers.[2]

The sequence of reactions employed to synthesize DL-α-lipoic acid in the present investigation may be represented as shown above.

An effective method of preparing mercapto acids consists of treating bromo esters with potassium thiolacetate in boiling ethanol, followed by hydrolysis of the resulting acetylmercapto esters.[4] We have applied this method successfully to the synthesis of DL-α-lipoic acid (VII) from ethyl 6,8-dibromoöctanoate (V). The latter substance was obtained by treatment of ethyl 6-oxo-7-octenoate (III) with anhydrous hydrogen bromide, followed by reduction with sodium borohydride to produce ethyl 8-bromo-6-hydroxyoctanoate (IV), which was converted to ethyl 6,8-dibromoöctanoate (V) with phosphorus tribromide. Treatment of the dibromo ester with potassium thiolacetate in boiling ethanol gave, after alkaline hydrolysis, 6,8-dimercaptoöctanoic acid (dihydro-α-lipoic acid) (VI). The latter compound was oxidized with iodine or with oxygen in the presence of ferric ion to give 60–68% yields of crystalline DL-α-lipoic acid (VII), based on the dibromo ester V. The average over-all yield of crystalline product, based on ethyl δ-chloroformylvalerate (I), was approximately 17%.

The dibromo ester V was converted in 82% yield to 6,8-dibenzylmercaptoöctanoic acid (X) by treatment with sodium benzylmercaptide in boiling ethanol, followed by alkaline hydrolysis. The product is a stable, crystalline compound which was readily reduced to 6,8-dimercaptoöctanoic acid (VI) with sodium in liquid ammonia. It is not necessary to isolate the dimercapto acid as the crude product can be oxidized in high yield to DL-α-lipoic acid.

Since 6,8-dibenzylmercaptoöctanoic acid is such a useful intermediate for preparing DL-α-lipoic acid or its dihydro form, an improved synthesis of this compound X was devised. It was found that under the conditions employed in the present investigation, ethyl δ-chloroformylvalerate (I) adds to ethylene in the presence of aluminum chloride to produce ethyl 8-chloro-6-oxoöctanoate (II) in good yield. Although the latter substance was not isolated, treatment of the crude product with sodium borohydride gave ethyl 8-chloro-6-hydroxyoctanoate (VIII) in 65–71% yield. The chlorohydrin VIII was converted in 80–85% yield to the dichloro

(3) Q. F. Soper, W. E. Buting, J. E. Cochran, Jr., and A. Pohland, THIS JOURNAL, 76, 4109 (1954).

(4) J. F. Danielli, M. Danielli, J. B. Fraser, P. D. Mitchell, L. N. Owen and G. Shaw, *Biochem. J.*, 41, 325 (1947); R. M. Evans and L. N. Owen, *J. Chem. Soc.*, 244 (1949).

ester IX with thionyl chloride. As observed by Evans and co-workers[5] with other dichlorides, ethyl 6,8-dichloroöctanoate does not react smoothly with potassium thiolacetate. However, it does react with sodium benzylmercaptide in boiling ethanol to give, after hydrolysis, 75–80% yields of 6,8-dibenzylmercaptoöctanoic acid (X). The average over-all yield of crystalline DL-α-lipoic acid *via* the dichloro ester IX was approximately 36%, based on ethyl δ-chloroformylvalerate (I).

The availability of ethyl 6,8-dibromoöctanoate and the corresponding dichloro ester makes S^{35}-labeled DL-α-lipoic acid easily accessible for use in biological experiments. A synthesis of this radioactive substance will be described elsewhere.

Experimental[6]

Ethyl 6-Oxo-7-octenoate (III).—This substance was prepared essentially according to the directions of Soper and co-workers.[3,7] Since vigorous evolution of hydrogen chloride occurs during distillation of ethyl 8-chloro-6-oxoöctanoate (II), we have found it desirable to insert a liquid nitrogen trap in the system, which serves the dual purpose of effectively trapping the hydrogen chloride and maintaining a constant pressure. In this Laboratory 72–80% yields of ethyl 6-oxo-7-octenoate were obtained, b.p. 112–114° (2 mm.), $n^{25}D$ 1.4485.[8]

Ethyl 8-Bromo-6-hydroxyoctanoate (IV).—A solution of 51.3 g. (0.28 mole) of ethyl 6-oxo-7-octenoate and 50 ml. of reagent-grade benzene was cooled in an ice-bath and shaken intermittently while anhydrous hydrogen bromide was passed into the solution. When 24.8 g. (0.31 mole) of hydrogen bromide had been absorbed, the flask was stoppered and allowed to stand at room temperature for 20 hours. The organic solvent was removed *in vacuo* and the reddish oil was dissolved in 200 ml. of 95% ethanol. This solution was maintained at 20° while a solution of 5.3 g. (0.14 mole) of sodium borohydride in 20 ml. of water was added dropwise with stirring (approximately 10 minutes). Forty milliliters of concentrated ammonium hydroxide was added, the cooling bath was removed, and stirring was continued for 30 minutes at room temperature.[9] The reaction mixture was poured into 500 ml. of water and the product extracted with two 150-ml. portions of ether. The combined ether extracts were washed with 50 ml. of 5% hydrochloric acid and dried over anhydrous sodium sulfate. The organic solvent was removed *in vacuo* and the oily residue distilled through a 6-in. Vigreux column. A small forerun (*ca.* 5 g.) was collected, followed by the main fraction, 41–48 g. (55–64%)[10]; b.p. 132–134° (0.5 mm.), $n^{25}D$ 1.4761. A sample was redistilled for analysis, b.p. 132° (0.5 mm.), $n^{25}D$ 1.4767.

Anal. Calcd. for $C_{10}H_{19}O_3Br$: C, 44.95; H, 7.17; Br, 29.91. Found: C, 45.04; H, 7.27; Br, 30.01.

Ethyl 6,8-Dibromoöctanoate (V).—A solution of 86 g. (0.32 mole) of ethyl 8-bromo-6-hydroxyoctanoate and 50 ml. of reagent grade carbon tetrachloride was maintained below 0° while 32 g. (0.12 mole) of phosphorus tribromide was added dropwise with stirring (approximately 25 minutes). Stirring was continued for 2 hours at 0° and the reaction mixture was allowed to stand at room temperature for 16 hours. At this time the reaction mixture was cooled to 0° and 70 ml. of cold water was added dropwise with stirring. Two hundred milliliters of ether was added and the mixture was shaken in a separatory funnel. The organic layer was washed successively with two 100-ml. portions of 5% sodium bicarbonate solution[11] and 50 ml. of water, and then dried over anhydrous sodium sulfate. The organic solvent was removed *in vacuo* and the oily residue distilled through a 6-in. Vigreux column. A small forerun (2–3 g.) was collected, followed by the main fraction, 58–67 g. (55–63%), b.p. 119–121° (0.4 mm.), $n^{25}D$ 1.4930. A sample was redistilled for analysis, b.p. 119° (0.4 mm.), $n^{25}D$ 1.4938.

Anal. Calcd. for $C_{10}H_{18}O_2Br_2$: C, 36.39; H, 5.50; Br, 48.42. Found: C, 36.71; H, 5.42; Br, 48.48.

Ethyl 8-Chloro-6-hydroxyoctanoate (VIII).—To a suspension of 108 g. (0.81 mole) of aluminum chloride in 450 ml. of reagent grade carbon tetrachloride was added dropwise, with vigorous stirring, 72 g. (0.37 mole) of ethyl δ-chloroformylvalerate.[12] The temperature was maintained at 25°. The cooling bath was removed and a rapid stream of ethylene was passed in for a period of 2 hours. The reaction mixture was poured onto cracked ice, the organic layer separated, and the aqueous layer extracted with 200 ml. of chloroform. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The dark-colored oil remaining[13] was dissolved in 200 ml. of 95% ethanol. This solution was stirred and maintained at 20° while a solution of 7.06 g. (0.19 mole) of sodium borohydride in 20 ml. of water was added dropwise. Concentrated ammonium hydroxide (40 ml.) was then added, the cooling bath was removed, and stirring was continued for 1 hour. The reaction mixture was poured into 500 ml. of water and the product extracted with two 150-ml. portions of ether. The combined ether extracts were washed with 50 ml. of 5% hydrochloric acid and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the oily residue distilled through a 6-in. Vigreux column. A small forerun was collected, followed by the main fraction, 54–59 g. (65–71%), b.p. 121–123° (0.5 mm.), $n^{25}D$ 1.4570. A sample was redistilled for analysis, b.p. 121° (0.5 mm.), $n^{25}D$ 1.4580.

Anal. Calcd. for $C_{10}H_{19}O_3Cl$: C, 53.93; H, 8.60; Cl, 15.92. Found: C, 54.20; H, 8.55; Cl, 16.27.

Ethyl 6,8-Dichloroöctanoate (IX).—A solution of 62.8 g. (0.28 mole) of ethyl 8-chloro-6-hydroxyoctanoate in 60 ml. of anhydrous benzene was added dropwise with stirring to a solution of 40 g. (0.34 mole) of thionyl chloride in 30 ml. of benzene containing four drops of pyridine. The reaction mixture was then heated under gentle reflux for 1 hour, cooled, and shaken with 100 ml. of ice-water. The organic layer was separated, dried over anhydrous sodium sulfate and distilled through a 6-in. Vigreux column. A small forerun was collected, followed by the main fraction, 54–58 g. (80–85%), b.p. 109–111° (0.7 mm.), $n^{25}D$ 1.4600. A sample was redistilled for analysis, b.p. 109° (0.7 mm.), $n^{25}D$ 1.4603.

Anal. Calcd. for $C_{10}H_{18}O_2Cl_2$: C, 49.80; H, 7.52; Cl, 29.41. Found: C, 50.16; H, 7.66; Cl, 29.33.

6,8-Dibenzylmercaptoöctanoic Acid (X).—To 150 ml. of absolute ethanol was added 5.06 g. (0.22 mole) of sodium. When all of the sodium had reacted, 27.3 g. (0.22 mole) of benzyl mercaptan and 24.1 g. (0.1 mole) of ethyl 6,8-dichloroöctanoate were added. The mixture was stirred and heated under reflux in an atmosphere of nitrogen for 14 hours. The reaction mixture was cooled to room temperature and 11.2 g. (0.17 mole) of potassium hydroxide was added. When the latter had dissolved, stirring was stopped and the reaction mixture was allowed to stand at room temperature for 20 hours. The reaction mixture was poured

(5) R. M. Evans, J. B. Fraser and L. N. Owen, *J. Chem. Soc.*, 248 (1949).

(6) Boiling points and melting points are uncorrected.

(7) We are indebted to Dr. Soper for making these directions available to us prior to publication.

(8) Q. F. Soper, *et al.*, ref. 3 report yields of 78–92%, b.p. 126–136° (8 mm.), $n^{25}D$ 1.4500. The pure material possessed b.p. 123–123.5° (8 mm.) and $n^{25}D$ 1.4493. M. W. Bullock, *et al.*, ref. 2, report a 48% yield by their method, b.p. 110–115° (2-3 mm.), $n^{25}D$ 1.4481 for pure material.

(9) This treatment with ammonium hydroxide is apparently an effective means of hydrolyzing the alkyl borate produced by the reduction with sodium borohydride.

(10) Use of ether as solvent or of benzoyl peroxide as catalyst in the reaction with hydrogen bromide did not materially affect the yield.

(11) An insoluble oil (approximately 29 g.) was obtained by acidification of the bicarbonate wash liquid. On the assumption that this acidic material was produced by hydrolysis of ethyl 8-bromo-6-hydroxyoctanoate or the dibromo ester, larger quantities of carbon tetrachloride as well as varying amounts of pyridine were employed in the reaction with phosphorus tribromide, without, however, materially altering the yield of dibromo ester. The nature of the acidic material was not investigated further.

(12) H. Bergs, S. Wittfeld and H. Frank, *Ber.*, **67B**, 1622 (1947). The ethyl hydrogen adipate employed was purchased from the Eastman Kodak Co.

(13) Distillation of this material *in vacuo* releases hydrogen chloride and yields ethyl-6-oxo-7-octenoate, as described previously.

into 500 ml. of water, acidified with 6 *N* hydrochloric acid and the product was extracted with two 150-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent was then removed *in vacuo*. A viscous oil remained which solidified when cooled and stirred. The solid material was dissolved in 105 ml. of warm benzene and 400 ml. of hot Skellysolve B[14] was added gradually. The clear solution was seeded with crystalline 6,8-dibenzylmercaptoöctanoic acid and allowed to stand overnight at room temperature and then in a refrigerator for several hours. The colorless crystals were collected on a büchner funnel and washed well with cold Skellysolve B. The yield was 29–31 g. (75–80%), m.p. 67.5–69°. A sample was recrystallized from benzene–Skellysolve B for analysis, m.p. 68–69°.[15]

Anal. Calcd. for $C_{22}H_{28}O_2S_2$: C, 68.00; H, 7.26; S, 16.56. Found: C, 67.89; H, 7.29; S, 16.55.

Ethyl 6,8-dibromoöctanoate was converted to 6,8-dibenzylmercaptoöctanoic acid in 82% yield by the procedure described above, with the exception that the period of reflux was only 5 hours.

6,8-Dimercaptoöctanoic Acid (Dihydro-α-lipoic Acid) (VI).—Sodium (6.9 g., 0.3 mole) was added in small portions to approximately 700 ml. of liquid ammonia. This solution was stirred while a solution of 38.8 g. (0.1 mole) of 6,8-dibenzylmercaptoöctanoic acid in 75 ml. of toluene was added dropwise during a 45-minute period. Toward the end of the reaction small pieces of sodium were added to maintain a permanent blue color. A total of 8.8 g. (0.38 mole) of sodium was employed. The blue color was discharged with ammonium chloride and the ammonia was allowed to evaporate overnight. The residue was extracted with 150 ml. of cold water and the organic layer was separated and discarded. The aqueous layer was acidified (*p*H < 1) with concentrated hydrochloric acid and extracted with three 50-ml. portions of chloroform. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The oily residue was distilled from a modified Claisen flask under reduced pressure in an atmosphere of carbon dioxide. Two colorless fractions were collected: a main fraction, 15.0 g., b.p. 160–162° (0.7 mm.), $n^{25}D$ 1.5231; and a center fraction, 2.0 g., b.p. 161.5° (0.7 mm.), $n^{25}D$ 1.5233.

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74; SH, 31.7. Found: C, 46.14; H, 7.85; SH, 31.2, 31.3.[16]

The main fraction also was analyzed for –SH; found 31.0. The total yield of 6,8-dimercaptoöctanoic acid was 17.0 g. (82%).

DL-α-Lipoic Acid (VII). Method A.—Thiolacetic acid[17] (14.7 g., 0.19 mole) was cooled in an ice-bath and neutralized to the phenolphthalein end-point with a 10% solution (w./v.) of potassium hydroxide in ethanol (approximately 135 ml. required). To this solution was added 29 g. (0.088 mole) of ethyl 6,8-dibromoöctanoate and the mixture was stirred and heated under reflux in an atmosphere of nitrogen for 5 hours. The reaction mixture was cooled, and 35 g. (0.53 mole) of potassium hydroxide was added. Stirring was continued until the potassium hydroxide had dissolved and the mixture was then allowed to stand at room temperature in an atmosphere of nitrogen for 17 hours. The reaction mixture was acidified (*p*H <1) with 6 *N* hydrochloric acid and concentrated *in vacuo* until an oily layer appeared. Sufficient water was added to dissolve the inorganic solids and the mixture was extracted with two 150-ml. portions of chloroform.[18] To the combined organic extracts were added 580 ml. of chloroform and 210 ml. of water. This mixture was stirred vigorously in an atmosphere of nitrogen while sufficient iodine–potassium iodide solution[19] was added dropwise during a 4-hour period to give a permanent brown color. Approximately 185 ml. was required. The organic layer was separated, washed with 500 ml. of 1% sodium thiosulfate solution, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The viscous yellow oil remaining solidified when cooled and stirred. This solid material was extracted with three 300-ml. portions of boiling Skellysolve B.[20] The combined extracts were seeded with crystalline DL-α-lipoic acid and allowed to stand at room temperature overnight and then in a refrigerator for several hours. Large yellow crystals separated, m.p. 60.5–61.5°. The yield of product was 10.8–12.3 g. (60–68%).[21] A sample was recrystallized from Skellysolve B for analysis, m.p. 61–62°. It possessed the characteristic ultraviolet absorption spectrum[22,23] of α-lipoic acid, $\lambda_{min.}$ 280 mμ, $\lambda_{max.}$ 332 mμ, $\epsilon_{max.}$ 157.

Anal. Calcd. for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.08. Found: C, 46.87; H, 6.73; S, 30.80.

Method B.—6,8-Dibenzylmercaptoöctanoic acid (19.4 g., 0.05 mole) was reduced with sodium in liquid ammonia as described previously. When the ammonia had evaporated the residue was extracted with 100 ml. of cold water. The aqueous layer was made acid to phenolphthalein and alkaline to litmus with 6 *N* hydrochloric acid, transferred to a 500-ml. graduated cylinder, and diluted to 400 ml. Two milliliters of 1% ferric chloride solution was added and a rapid stream of oxygen was bubbled through the solution from a sintered glass tube until the reddish color changed to pale yellow (approximately 6 minutes). The solution was acidified and the product extracted with two 100-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The viscous yellow oil solidified on standing. The solid was extracted with one 400-ml. portion and one 200-ml. portion of boiling Skellysolve B. The extracts were treated as described previously to yield 8.44–8.74 g. (82–85%)[24] of bright yellow crystals, m.p. 61–62°; mixture with sample prepared by method A, m.p. 61–62°.

Acknowledgments.—We are indebted to Dr. C. G. Skinner and staff of the Biochemical Institute for the C and H analyses and to the Clark Microanalytical Laboratory, Urbana, Illinois, for the S analyses.

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(14) A *n*-hexane fraction, b.p. 60–68°, obtained from the Skelly Oil Co., Kansas City, Missouri.

(15) Q. F. Soper, *et al.*, ref. 3, report m.p. 63–65° for material which was still impure, as indicated by the analytical data presented.

(16) Determined by the iodine method of J. W. Kimball, R. L. Kramer and E. E. Reid, THIS JOURNAL, **43**, 1199 (1921), as adapted by S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 85.

(17) Eastman Kodak practical grade was redistilled before use, b.p. 86–87°.

(18) 6,8-Dimercaptoöctanoic acid (dihydro-α-lipoic acid) was obtained in 72% yield by distillation of the oil remaining after removal of the chloroform, b.p. 154–156° (0.3 mm.), $n^{25}D$ 1.5249, SH, 30.7. The product was pale yellow in color and not as pure as that obtained from 6,8-dibenzylmercaptoöctanoic acid.

(19) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 53.

(20) Varying amounts of a "polymeric" material remain after extraction with Skellysolve B. This material, which may be a linear disulfide produced by oxidation of 6,8-dimercaptoöctanoic acid, contains DL-α-lipoic acid, as indicated by a yellow color. The DL-α-lipoic acid can be recovered by extraction with benzene, in which the "polymer" is insoluble.

(21) The yield of crystalline DL-α-lipoic acid was approximately the same when the crude 6,8-dimercaptoöctanoic acid, obtained by evaporation of the chloroform extracts, was oxidized in alkaline solution with oxygen in the presence of ferric ion (see Method B below).

(22) M. Calvin and J. A. Barltrop, THIS JOURNAL, **74**, 6153 (1952).

(23) L. J. Reed, I. C. Gunsalus, G. H. F. Schnakenberg, Q. F. Soper, H. E. Boaz, S. F. Kern and T. V. Parke, *ibid.*, **75**, 1267 (1953).

(24) Somewhat lower yields were obtained by oxidation with iodine–potassium iodide solution as in method A. As reported by W. M. Bullock, *et al.*, ref. 2, oxidation of 6,8-dimercaptoöctanoic acid with oxygen in the presence of ferric ion is the superior procedure.