

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 $C_8H_{16}O_2S_2$: 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 pH 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_D^{20} 1.4610.

Anal. Calcd. for $C_{12}H_{20}O_2$: 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_D^{20} 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.

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Convenient Synthesis of Thioctic Acid

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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 expen-

sive 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-oxooctanoic 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 Acker⁸ 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-

(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, Jr., J. W. Cochran, Jr., and A. Pohl and, *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).

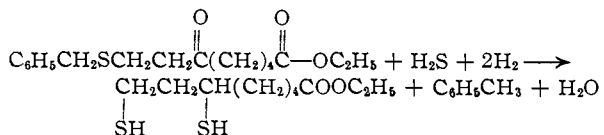
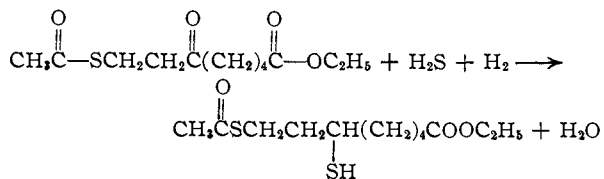
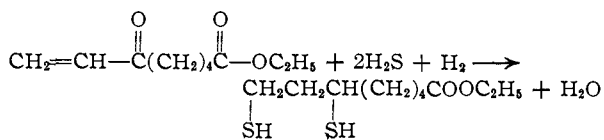
(5) E. Walton, A. F. Wagner, F. A. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5144 (1955).

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

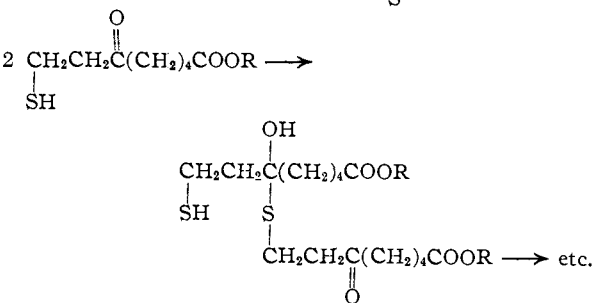
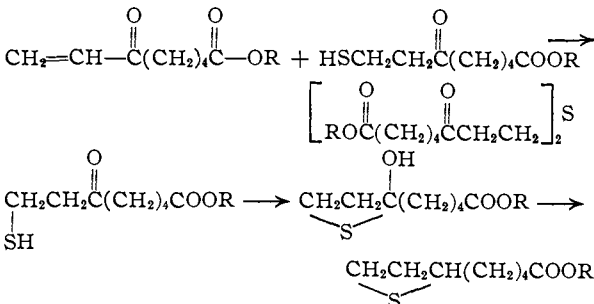
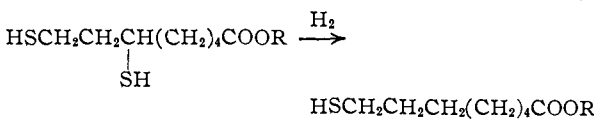
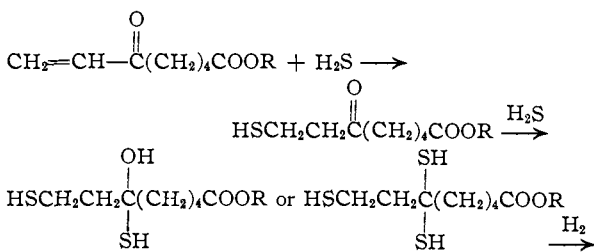
(7) M. W. Bullock, J. J. Hand and E. L. R. Stokstad, *THIS JOURNAL*, **79**, 1975 (1957).

(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).



The most readily available and least expensive starting materials are the vinyl ketones which probably react as



pear to be the most prominent. The side reaction involving the addition of the first formed β -thiolketone to the unreacted vinyl ketone is a major side reaction unless a large excess of hydrogen sulfide is used. It is apparent that a high concentration of hydrogen sulfide will also minimize other side reactions except for the formation of the monothiol by hydrogenolysis of a thiol group.

This reaction is favored by high temperature and high pressure. The reduction is best carried out at the lowest practical temperature and pressure—150–160° at 100 atm. pressure. The use of a large amount of catalyst is highly desirable.

Somewhat better yields can be obtained when the acetylthio ketone replaces the vinyl ketone. The increase presumably is due to a decrease in the formation of by-products. The acetyl group, if not hydrolyzed during the reaction, is readily removed during the esterification of the crude products so that the same product is obtained.

The benzylthio ketone would appear to be a most desirable starting material since the benzyl group can be removed by hydrogenolysis. However, in our hands, we have found it difficult to reduce this group without considerable hydrogenolysis of the secondary thiol group.

The use of the methyl or ethyl 6,6,8-tris-benzylthio ester appears to offer no advantage over the corresponding ketone. A mixture of methyl 8-benzylthio-6-oxooctanoate and α -toluenethiol are equivalent to the tris-benzylthio compound. It is probable that the tris compound is formed *in situ* and subsequently reduced to the same products.

On the basis of our limited experience with thiones it would appear that this class of compound is reduced with as much or more difficulty as their oxygen analogs.

At the temperatures and pressures necessary for the reduction, ester exchange occurs so that the material present at the end of the reduction is dependent on the solvent used. For example, in the presence of excess acetic acid the ketoester added as starting material will be converted largely to the free acid, and a corresponding amount of the acetic acid will be esterified. At first it was believed that the hydrolysis of the starting material was caused by the water formed in the reduction. Addition of acetic anhydride to take up the water appeared to retard the reduction rate with no decrease in the amount of free acid formed. Attempts to substitute dioxane, xylene, ethyl acetate, methanol or ethanol for the acetic acid were unrewarding. Although the latter two solvents solved the hydrolysis problem, the reduction rate appeared to be slower in all these solvents.

When acetic acid is employed as the solvent, the reduction product as taken from the bomb will have been largely converted to the acid. The most satisfactory procedure is to esterify the crude product and purify by careful fractionation of the ester. Attempts to purify crude acids by distillation have been most unrewarding since the crude dithiol acids do not distill well. However, small quantities of purified dithiol acids are readily distillable.

There are several known catalysts capable of effecting the reduction of various sulfur compounds to thiols. The preparation of cobalt polysulfide catalyst and others has been described by Farlow, *et al.*¹⁰ Other catalysts are described by Cope and Farkas.¹¹ Cope and Farkas used their cat-

(10) M. W. Farlow, W. A. Lazler and F. S. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

(11) A. C. Cope and E. Farkas, *J. Org. Chem.*, **19**, 385 (1953).

alysts principally for hydrogenation of thiols to hydrocarbons. This is the same type of reaction employed for the reduction to the thiol and so these catalysts will presumably be operative in this process.

The entire success of the operation depends on getting an active preparation. With an active catalyst the hydrogen uptake will be apparent when the temperature reaches 125°, and be sufficiently rapid at 150° to raise the temperature of the bomb several degrees. The cobalt polysulfide catalyst used for all our reductions is, according to Farlow, *et al.*, precipitated from the solution as an inactive form. When this catalyst is heated in a reducing atmosphere it is converted into an active form, which is pyrophoric. Cope and Farkas describe their cobalt sulfide catalyst as pyrophoric when dried *in vacuo* without the heating in a reducing atmosphere. Our preparations, which are obtained and used as an acetic acid paste, have never been pyrophoric. These catalysts generally do not retain their activity for many days even when stored in a closed bottle. We have found it advantageous to prepare the catalyst the day before or on the same day that it is to be used. A typical preparation is given in detail in the Experimental section.

It might be mentioned here that the corrosion of the bomb is not negligible when acetic acid is used as the solvent. All other solvents caused less corrosion but, as mentioned above, are largely unsatisfactory. Copper gaskets and brass supports for the glass liner, if any, are severely attacked and should never be employed. We have used stainless steel supports for our glass liner several times without encountering any difficulties.

Summary of Recommended Operating Procedure: (1) Use large excess of sulfur. A 200% excess appears to give fairly satisfactory results.

(2) Use large amounts of freshly prepared catalyst in the form of approximately 20% acetic acid paste. The catalyst should not have been standing longer than one day. The minimum quantity recommended is 0.25 mole of cobalt polysulfide per mole of ketone. The reduced form of the catalyst is alleged to be pyrophoric and is inactivated by exposure to air.

(3) Fill bomb to 100 atm. pressure and heat rapidly with shaking to 125°. Shut off heat as the reduction will be sufficiently rapid to raise the temperature to about 150° while the sulfur is being hydrogenated to hydrogen sulfide. Refill whenever the hydrogen pressure drops below 34-40 atm.

If it is desired to measure the hydrogen used it is necessary to stop the shaker during the filling operation as a large amount of hydrogen will be taken up during the filling operation. At 150° the pressure will generally drop from 100 to 40 atm. in five to ten minutes. The rate of temperature rise is determined by the rate hydrogen is being added; should the temperature rise above 155° the addition of more hydrogen should be stopped until it begins to drop. When all the sulfur has been converted to hydrogen sulfide there will be an abrupt drop in the rate. The bomb is then heated to 150-160°

and the pressure maintained at 100 to 55 atm. until the hydrogen uptake stops. If benzylthio intermediates are used, the temperature should be increased to 175° after the rapid hydrogenation stops for about two hours and finally to 200° for two to three hours to effect complete hydrogenolysis of the benzyl group.

(4) The catalyst is removed by filtration and washed with methanol or acetic acid. The acetic acid, which is the preferred solvent for the reduction, is distilled off and the product esterified with methanol. The ester, after isolation from the methanol, should be carefully fractionated at reduced pressure. If the product is cleaned up at this stage no difficulty will be experienced in obtaining an easily crystallized final product.

(5) The ester is saponified with aqueous sodium hydroxide and the pH adjusted to 7. The volume is diluted so that the concentration of the acid salt is about 10%. Now approximately 5 ml. of 10% ferric chloride hexahydrate per liter of solution is stirred in. If the resulting solution is not translucent it may be filtered through diatomaceous earth. A stream of oxygen is passed into the rapidly stirred solution through a sintered glass inlet tube until the purple solution changes to light yellow. The pH of the solution should be checked at frequent intervals and acid added if necessary to keep the solution near neutrality. If the solution is permitted to become alkaline some of the disulfide will be oxidized to the thiosulfinate, which is then hydrolyzed in part to yield more thiol and eventually polymer-like materials are formed which prevent the crystallization of the product. The preferred procedure for recovery of the oxidized material from the aqueous solution is to add ethyl acetate and slowly acidify the stirring mixture. This method appears to give less tarry materials than acidifying the aqueous phase and extracting the precipitated oil with a solvent. Distillation of the solvent will generally yield a crystalline product if a purified ester is used. The disulfide acids can be distilled if not obtained in crystalline form. The most satisfactory solvent for recrystallizing thioctic acid is *n*-butyl ether (3 ml./g. of acid). The butyl ether must be free of peroxides which cause polymerization. The ether solution should not be heated above about 45° until all crystals have dissolved. The crystallization should be allowed to proceed at a temperature of about 25°. At lower temperatures poor crystals are frequently obtained.

Acknowledgment.—The authors are indebted to Mr. L. Brancone and staff for the microanalyses and to Mr. J. L. Sanjurjo who carried out many of the hydrogenations.

Experimental

Preparation of Cobalt Polysulfide Catalyst.—A solution of sodium polysulfide prepared by dissolving 240 g. (1 mole) of sodium sulfide nonahydrate and 64 g. (2 moles) of sulfur in 900 ml. of water was added all at once to a rapidly stirring solution of 238 g. (1 mole) of cobalt chloride hexahydrate in 500 ml. of water. The suspension of the black precipitate was stirred rapidly for three minutes and poured into a 24-cm. Büchner funnel containing four sheets of filter paper. The cake was washed with water until the pink color in the filtrate disappeared and then with glacial acetic acid. The cake was squeezed as dry as possible by stretching a sheet

of rubber dam over the top of the funnel. The resulting cake contains about 20% solids. If not used immediately it was stored in sealed containers at 0°. The activity of the catalyst decreases greatly on storage of several days. However, no detectable decrease in activity has been noticed on storage overnight.

Preparation of Thioctic Acid from Methyl 6-Oxo-7-octenoate.—A 1410-ml. stainless steel hydrogenation bomb was charged with 170.2 g. (1 mole) of methyl 6-oxo-7-octenoate, 0.5 mole of freshly prepared cobalt polysulfide-acetic acid paste, 96 g. (3 moles) of sulfur and sufficient acetic acid to bring the volume to 690 ml. The bomb was filled with hydrogen to 94 atm. The bomb was shaken and heated to 150°. By the time the temperature had reached about 125° the reduction had started, and the pressure had dropped to 36 atm. by the time the temperature reached 149°. More hydrogen was added at 5- to 10-minute intervals until the rapid hydrogenation uptake stopped. The temperature rose to 153° from the heat of reaction as 4.6 moles were taken up in 15 minutes. The temperature was maintained at about 150° and the pressure 92-75 atm. for six hours during which time an additional 0.61 mole of hydrogen was used bringing the total calculated hydrogen consumption to 5.2 moles (theory 5 moles). The bomb was allowed to cool, and the catalyst was filtered off and washed with acetic acid. The acetic acid was distilled off under reduced pressure. The residue was taken up in 400 ml. of methanol containing 5 ml. of sulfuric acid and refluxed 90 minutes. Most of the methanol was distilled off under reduced pressure and the residue poured into a mixture of ice and ethyl acetate. The organic layer was separated, washed with saturated sodium bicarbonate solution and with water. The solvent was distilled leaving 174.1 g. of oil which was distilled *in vacuo*. The fractions distilling 142-160° at 4.3-3.2 mm. and weighing 102 g. were collected as product.

The crude methyl 6,8-dithiooctanoate was saponified by refluxing two hours with a solution of 20.3 g. of sodium hydroxide in 500 ml. of water. The solution was adjusted to pH 7 and extracted with ethyl acetate. The aqueous solution was diluted to one liter and 10 ml. of 10% ferric chloride hexahydrate and approximately 20 g. of sodium bicarbonate was added. Oxygen was passed through the rapidly stirred solution until the color changed from purple to light yellow (20 minutes). Approximately 200 ml. of ethyl acetate was added and the solution acidified with hydrochloric acid. The ethyl acetate layer was separated, dried over sodium sulfate and distilled. The oily residue was distilled *in vacuo* and the fraction b.p. 150-160° at 0.1 mm. and crystallizing in the receiver collected as product. These crude crystals, weight 79.8 g., were recrystallized from 240 ml. of *n*-butyl ether to yield 46.2 g. of pure product, m.p. 60.5-61°. Concentration of the mother liquor yielded an additional 15.1 g. bringing the yield of recrystallized material to 67.7 g. (0.298 mole), 29.8%.

Bis-(7-Carboxy-3-oxooctanyl) Sulfide.—A sample of this material was isolated from the very high boiling residues and purified by recrystallization from methanol. The pure material had m.p. 80-82°.

Anal. Calcd. for C₁₆H₂₆O₈S: C, 55.47; H, 7.56; S, 9.25. Found: C, 55.74; H, 7.91; S, 9.03.

Preparation of Thioctic Acid from Methyl 8-Acetylthio-6-oxooctanoate.—A 1410-ml. stainless steel hydrogenation bomb was charged with 246.3 g. (1 mole) of methyl 8-acetylthio-6-oxooctanoate, 96 g. (3 moles) of sulfur and 0.5 mole of cobalt polysulfide-acetic acid paste which had been prepared the day before. Acetic acid was added to render the reaction mixture sufficiently fluid for shaking. The bomb was filled with hydrogen to 80 atm. pressure and shaken while the temperature was increased slowly. By the time the temperature was 135° the pressure had dropped to 48 atm. The bomb was filled at about 5-minute intervals until the rapid uptake of hydrogen stopped. The temperature rose to 150° during the absorption of 4.4 moles of hydrogen over a period of 40 minutes. The temperature was maintained at 150° for 1.5 hours and at 160° for two hours. Hydrogen was added occasionally to bring the pressure back to 75 atm. The total hydrogen uptake was 5.4 moles (theory 5). The bomb was allowed to cool and the catalyst was filtered off and washed with methanol. The solvents were distilled off and the residue taken up in 350 ml. of methanol containing 30 g. of hydrogen chloride. The resulting solution was refluxed two hours and the methanol

distilled off under the reduced pressure. The residue was taken up in 500 ml. of ethyl acetate and washed with water and with saturated sodium bicarbonate solution. The ethyl acetate solution was dried over sodium sulfate and the solvent distilled. The residue was distilled through a 12" electrically heated Vigreux column. The fraction distilling 136-140° at 3.5-2 mm. was collected as product.

The yield of the ester based on these cuts was 162.3 g. (0.74 mole) or 74%. This crude ester was saponified by refluxing two hours with 200 ml. of 5 *N* sodium hydroxide in 1 liter of water. The pH was adjusted to 7 and the aqueous solution washed once with ethyl acetate. Ten ml. of 10% ferric chloride hexahydrate was mixed with 50 ml. of 95% ethanol, and added to the aqueous solution. The volume was diluted to 2.5 liters and a rapid stream of oxygen bubbled through the rapidly stirred solution until the color changed from purple to light brown (15 minutes). Now 500 ml. of ethyl acetate was added and the stirring solution slowly acidified with 12 *N* hydrochloric acid. The ethyl acetate layer was separated, dried (Na₂SO₄), and distilled leaving 145 g. of crude thioctic acid which was purified by vacuum distillation. The fraction distilling 142-160° at 0.1 mm., wt. 109.8 g. (0.544 mole), was collected as product. These slightly oily crystals were recrystallized from 300 ml. of *n*-butyl ether to yield 79.2 g. (0.385 mole) of clean yellow crystals, m.p. 59°. The yield of purified product was 38.5% based on methyl 8-acetylthio-6-oxooctanoate.

Methyl 6,8-Dimercaptooctanoate.—A small sample of the intermediate ester was purified by careful fractionation through a Podbielniak Heli-grid column. The pure ester, b.p. 172° at 1 mm., had *n*_D²⁰ 1.5060 and *d*₄²⁰ 1.040.

Anal. Calcd. for C₉H₁₈O₂S₂: C, 48.61; H, 8.16; S, 28.84. Found: C, 48.96; H, 8.35; S, 28.91.

Methyl 8-Benzylthio-6-oxooctanoate.— α -Toluenethiol (185 g., 1.5 moles) and about 50 mg. of sodium hydride were allowed to interact. After most of the sodium hydride had reacted 244 g. (1.43 moles) of methyl 6-oxo-7-octenoate was added. After the exothermic reaction had subsided the reaction mixture was heated on the steam-cone one hour. The reaction mixture was cooled, diluted with an equal volume of chloroform and washed once with water. The chloroform was dried over sodium sulfate and the solvent distilled. Distillation yielded 303.4 g. (1.03 moles, 72%) of material, b.p. 175° at 0.1 mm., *n*_D²⁰ 1.5291 and *d*₄²⁰ 1.100.

Anal. Calcd. for C₁₆H₂₂O₃S: C, 65.27; H, 7.53; S, 10.89. Found: C, 64.87; H, 7.56; S, 11.17.

Ethyl 8-Benzylthio-6-oxooctanoate.—The ethyl ester was prepared in 80-89% yields by the same procedure as the methyl ester described above. The product distilled 184° at 0.1 mm. and had *n*_D²⁰ 1.5232.¹²

Anal. Calcd. for C₁₇H₂₄O₃S: C, 66.22; H, 7.84; S, 10.40. Found: C, 65.86; H, 8.00; S, 10.34.

Preparation of Thioctic Acid from Methyl 8-Benzylthio-6-oxooctanoate.—A hydrogenation bomb equipped with a glass liner was charged with 147.2 g. (0.5 mole) of methyl 8-benzylthio-6-oxooctanoate, 61 g. (1.9 moles) of sulfur, 61.3 g. (0.6 mole) of acetic anhydride, 200 g. of 20% cobalt polysulfide-acetic acid paste and 350 ml. of acetic acid. The hydrogenation bomb was filled to 87 atm. and heated to 170° over a period of 2 hours. The temperature was maintained at 170-175° and the pressure at 87 to 51 atm. for 4 hours and then at 190° for 1 hour. The total hydrogen uptake, which was rather slow, amounted to 2.5 moles. The catalyst was removed by filtration and washed with acetic acid. Distillation of the solvent left an oil which was distilled under reduced pressure. The fractions distilling 127-160° at 0.12 mm. and 130-158° at 0.07 mm. were taken as the product. The lower boiling fraction, most of which distilled 129° at 0.12 mm. and weighed 26.5 g., was saponified with potassium hydroxide to yield 23 g. of acid. The higher boiling fraction, most of which distilled at 158° at 0.07 mm. and weighed 29.3 g., was found to be an acid. It was dissolved in dilute base and the pH adjusted to 7. Extraction of the aqueous solution with ether removed a small amount of insoluble material. Recovery of the acid gave 26 g. of oil. The combined acid fractions were oxidized in water solution as described before, recovered and distilled to yield 37.8 g. of material, b.p. 140-160° at 0.06 mm. The largely crystalline product was stored at 0° two

(12) Soper, *et al.*, ref. 2, reported that the addition product was not distillable.

days with 25 ml. of *n*-butyl ether. The yellow crystals, m.p. 59–60°, were filtered off, washed with cyclohexane and with ligroin and air-dried. The yield was 27 g. (0.131 mole), 26.2%.

Preparation of Thioctic Acid from Methyl 6,6,8-Trisbenzylthiooctanoate.—A stainless steel hydrogenation bomb was charged with 1.61 moles of crude methyl 6,6,8-trisbenzylthiooctanoate¹⁸ and 0.125 mole of cobalt polysulfide acetic acid paste, and shaken with hydrogen at an initial pressure of 116 atm. at 150–160° for 2.5 hours. The temperature was increased to 175° for 2.5 hours and to 180° for 2 hours. Hydrogen was added from time to time to keep the pressure between 54 and 116 atm. The total hydrogen uptake was 6.3 moles (theory 5.9). The catalyst was removed by filtration and washed with methanol. The filtrate was freed of solvents under reduced pressure. The residue was taken up in 300 ml. of methanol containing 5 ml. of sulfuric acid and refluxed two hours. The methanol was distilled off at the water-pump. The residue was taken up in ethyl acetate and washed with water and with sodium bicarbonate solution. The residue was subjected to vacuum distillation. The products were collected as follows in two main fractions. The first fraction distilled 87° at 0.5 mm. (190° at 760 mm.) and weighed 172 g. This was found to be α -toluene thiol. The second fraction distilled 87–180° at 0.05–0.15 mm. and weighed 177 g. The residue weighed 290 g. The second fraction was combined with the residue and rehydrogenated using 0.125 mole of cobalt polysulfide-acetic acid paste catalyst and 150 ml. of acetic acid as solvent. The reduction was carried out for 7 hours at 200° with hydrogen pressures of 68–110 atm.; 2.5 moles was taken up. The contents of the cooled bomb were worked up as above and this rehydrogenated material distilled through a 12" Stedman column to yield three fractions: (1) b.p. 102–108° at 3.8 mm., wt. 20.8 g.; (2) b.p. 116–120° at 3.8 mm., wt. 14.8 g.; (3) b.p. 153–155° at 3.8 mm., wt. 69.3 g.

The first fraction was refractionated through the same column. The bulk of the material distilled 113–114° at 5.8 mm. The apparently pure material had n_D^{20} 1.4645.

Anal. Calcd. for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03; sapn. equiv., 188.28. Found: C, 57.35; H, 8.86; S, 17.58; sapn. equiv., 203.

The second fraction was refractionated through a 6" Helipak column. This gave a pure component distilling 110° at 3.2 mm. and having n_D^{20} 1.4735.

Anal. Calcd. for $C_9H_{16}O_2S$: C, 56.80; H, 9.53; S, 16.85; sapn. equiv., 190.28. Found: C, 57.46; H, 10.20; S, 16.85; sapn. equiv., 135.5.

Neither of the low boiling fractions was characterized. The third fraction was converted to thioctic acid by the procedures described above and distilled yielding 32 g. of yellow oil which crystallized when cool. The product was recrystallized from 100 ml. of *n*-butyl ether to yield 20.0 g. (0.096 mole, 6%) of pure thioctic acid, m.p. 60–61°.

Preparation of Thioctic Acid from Methyl 8-Benzylthio-6-oxo-octanoate and α -Toluene Thiol.—A stainless steel hydrogenation bomb was charged with 294.4 g. (1 mole) of methyl 8-benzylthio-6-oxo-octanoate, 186.3 g. (1.5 moles) of α -toluene thiol, 0.125 mole of cobalt polysulfide-acetic acid paste, a small amount of acetic acid, and hydrogen to 110 atm. After about three hours shaking at 175° the pressure had dropped to 54 atm. The bomb was again filled with hydrogen and the temperature increased to 200°. Hydrogen was added occasionally to keep the pressure between 80 and 110 atm. After 6 hours total reaction time the hydrogen uptake was 3.24 moles (theory 3 moles) and the reaction was stopped. The catalyst was removed by filtration and washed with methanol. The solvents were distilled off and the residue taken up in 300 ml. of methanol containing 5 ml. of sulfuric acid. The resulting solution was refluxed 90 minutes and the excess methanol distilled

off. The residue was taken up in ethyl acetate and washed with water and sodium bicarbonate solution. The solvent was distilled off and the residue distilled *in vacuo*, to yield 121.7 g. of crude ester, b.p. 102–135° at 0.2 mm. The ester was converted to thioctic acid as described above to yield 40 g., 19.5% of recrystallized acid.

Preparation of Methyl 8-Benzylthio-6-thio-octanoate.—A mixture of 262 g. (0.895 mole) of methyl 8-benzylthio-6-oxo-octanoate and one liter of methanol was stirred and cooled in an ice-bath while a stream of hydrogen chloride and hydrogen sulfide was passed through for 5 hours. The stirrer was stopped but the gas stream was passed into the two-phase mixture overnight. The reaction mixture which had warmed to room temperature during the night was stirred into 3 liters of ice and water. The red oily product was extracted with ether. The ether solution was washed with water and with sodium bicarbonate solution. The ether extract was dried over sodium sulfate and distilled leaving 269 g. (0.865 mole, 97%) of orange oil which showed no tendency to crystallize.

Anal. Calcd. for $C_{16}H_{22}O_2S_2$: S, 20.30. Found: S, 19.38.

Preparation of Thioctic Acid from Methyl 8-Benzylthio-6-thio-octanoate.—A mixture of 164 g. (0.528 mole) of methyl 8-benzylthio-6-thio-octanoate, 0.125 mole of cobalt polysulfide-acetic acid paste and 350 ml. of dioxane was hydrogenated as described above. The reduction was very slow, and after 6.5 hours reaction time the hydrogen uptake was only 0.75 mole (theory 1.06). The catalyst was removed by filtration and washed with methanol. The solvents were distilled off, the residue poured into 300 ml. of methanol containing 5 ml. of sulfuric acid, and the resulting solution was refluxed 90 minutes and most of the methanol distilled off under reduced pressure. The residue was taken up in ethyl acetate and washed with water and with sodium bicarbonate solution. The solvent was removed and the oily residue distilled *in vacuo*. The fraction distilling 120–135° at 0.2 mm. and weighing 14.2 g. was collected as product. The crude ester was converted to thioctic acid as described above to yield 5.1 g., 4.7%, of slightly impure acid, m.p. 55–57°.

Preparation of 8-Methylthioctic Acid (5-Methyl-1,2-dithiolane-3-valeric Acid) from Methyl 6-Oxo-7-nonenolate.—A mixture of 106.4 g. (0.58 mole) of methyl 6-oxo-7-nonenolate,⁸ 55.5 g. (1.74 moles) of sulfur, 0.5 mole of cobalt polysulfide-acetic acid paste catalyst and sufficient acetic acid to make the mixture sufficiently fluid for slaking was hydrogenated as above. The hydrogen uptake was 3.30 moles (theory 3.31). The catalyst was removed by filtration, the solvents were removed under the reduced pressure and the residue was taken into 250 ml. of methanol containing 10 ml. of sulfuric acid and refluxed 2 hours. Most of the methanol was distilled off. The residue was taken up in ethyl acetate and washed with water and sodium bicarbonate solution. Distillation of the solvent left an oil which was distilled through a 6" Helipak column. The fraction distilling 134–141° at 3 mm. and weighing 51 g. was collected as product. There were 46.3 g. of forerun and 10.5 g. of residue.

The methyl ester was saponified by refluxing two hours with a solution of 100 ml. of 5 *N* sodium hydroxide in 200 ml. of water. The excess base was neutralized to pH 7 and the aqueous solution extracted with 200 ml. of ethyl acetate. The volume of the aqueous solution was adjusted to 1 liter and 5 ml. of 10% ferric chloride hexahydrate was added. The resulting deeply colored solution was oxidized by passing a stream of oxygen through the rapidly stirred solution until the dark color disappeared (10 minutes). Ethyl acetate was added and the solution was acidified. The organic layer was separated, dried over sodium sulfate, and the solvent distilled. The oily residue on cooling crystallized to yellow crystals, m.p. 44–47°. The yield was 46 g. (0.209 mole), 36.1% of product, m.p. 53.55° after two recrystallizations from *n*-butyl ether. A mixed melting point with the compound prepared through the 6-hydroxy compound was not depressed.⁷

(13) The methyl 6,6,8-trisbenzylthiooctanoate was prepared by methods similar to that described by Soper, *et al.*, ref. 2. It was an oil which was not purified.