

5,7-Dichloroheptyl Thiolacetate (IV).—Thiolacetic acid (15.6 g., 0.21 mole) was cooled in an ice-bath and neutralized to the phenolphthalein end-point with a 2.5 *N* solution of potassium ethoxide in ethanol (approximately 81 ml. required). The resulting suspension was added in portions to a solution of 51 g. (0.21 mole) of 7-bromo-1,3-dichloroheptane in 80 ml. of ethanol. During the addition (2.5 hours) the reaction mixture was stirred and maintained under reflux in an atmosphere of nitrogen. Stirring and heating were continued for an additional 4 hours. The reaction mixture was cooled, filtered, and the filtrate was poured into 750 ml. of water. 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 removed *in vacuo*. The oily residue was distilled through a 6-in. Vigreux column to yield 38.5 g. (77%) of product; b.p. 116–120° (0.55 mm.); n_D^{20} 1.5032; $\lambda_{\max}^{95\% \text{ ethanol}}$ 232 μ (ϵ 4640).

Anal. Calcd. for $C_9H_{16}Cl_2OS$: C, 44.45; H, 6.63; Cl, 29.16; S, 13.19. Found: C, 44.73; H, 6.64; Cl, 29.38; S, 13.55.

5,7-Dichloroheptanesulfonamide (V).—A suspension of 5 g. (0.02 mole) of 5,7-dichloroheptyl thiolacetate in 100 ml. of water was stirred vigorously and maintained below 3° during the introduction of chlorine. When the reaction mixture became yellowish green in color, indicating an excess of chlorine, it was extracted with ether. The ether extract was washed successively with cold 5% sodium bisulfite solution, 5% sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was stirred and heated at 60° for 1 hour with 40 ml. of concentrated ammonium hydroxide. The product was extracted into ether and the ether extract was dried and then evaporated *in vacuo*. The solid residue was crystallized from dilute ethanol to yield 3.13 g. (63%) of 5,7-dichloroheptanesulfonamide, m.p. 72–73°. A sample was recrystallized for analysis, m.p. 74–75°.

Anal. Calcd. for $C_7H_{15}Cl_2NO_2S$: C, 33.85; H, 6.09; Cl, 28.57; N, 5.64. Found: C, 34.22; H, 6.29; Cl, 28.72; N, 5.59.

5,7-Di-(benzylthio)-heptanesulfonamide (VI).—To 2.97 g. (0.012 mole) of 5,7-dichloroheptanesulfonamide was added 3.23 g. (0.026 mole) of benzyl mercaptan and 20 ml. of a 1.3 *N* solution of sodium ethoxide in absolute ethanol. The mixture was stirred and heated under reflux in an atmosphere of nitrogen for 14 hours. The reaction mixture was cooled, poured into 150 ml. of water, and the mixture was extracted with ether. The aqueous layer was acidified and the product extracted into ether. The ether extract was dried over anhydrous sodium sulfate and then the solvent was removed *in vacuo*. The oily residue was crystallized from benzene-

Skellysolve B¹³ to yield 3.51 g. (69%) of product. A sample was recrystallized for analysis, m.p. 67.5–68°.

Anal. Calcd. for $C_{21}H_{39}NO_2S_2$: C, 59.50; H, 6.90; N, 3.31; S, 22.71. Found: C, 59.41; H, 7.08; N, 3.33; S, 22.80.

DL-1,2-Dithiolane-3-butanefulfonamide (VII).—5,7-Di-(benzylthio)-heptanesulfonamide (3.0 g., 0.0069 mole) was reduced with sodium in liquid ammonia in a manner described previously.⁵ After removal of the ammonia 50 ml. of water was added to the residue and the mixture was extracted with 30 ml. of ether. The aqueous layer was adjusted to pH 11.5 and 0.2 ml. of 1% ferric chloride solution was added. A rapid stream of oxygen was bubbled through the solution from a sintered glass tube until the reddish color changed to pale yellow (approximately 15 minutes). The solution was acidified and the mixture was extracted with three 15-ml. portions of chloroform. Yellow chloroform extracts and an insoluble, gray polymeric material were obtained. The polymeric material was warmed on a steam-bath with 20 ml. of 0.5 *N* sodium hydroxide until it dissolved (approximately 10 minutes). The resulting bright yellow solution¹³ was acidified and the yellow oil extracted with two 15-ml. portions of chloroform. These chloroform extracts were combined with those obtained as described above and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the bright yellow residue was extracted with 20 ml. of warm benzene. When the benzene solution was cooled, 768 mg. (45%) of yellow crystals separated, m.p. 65–67°. To the filtrate was added 8 ml. of Skellysolve B. When this solution was cooled, 160 mg. (9%) of yellow crystals was obtained, m.p. 65–67°. A sample was recrystallized for analysis; m.p. 68–69°; $\lambda_{\max}^{95\% \text{ ethanol}}$ 332 μ (ϵ 157), λ_{\min} 280 μ .

Anal. Calcd. for $C_7H_{15}NO_2S_2$: C, 34.80; H, 6.26; N, 5.80; S, 39.85. Found: C, 35.11; H, 6.24; N, 6.04; S, 39.89.

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

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

(13) It has been observed that sticky, colorless polymers are produced as by-products in the oxidation of DL-6,8-dithiolactanoic acid to the cyclic disulfide, DL- α -lipoic acid (ref. 5), and also when the cyclic disulfide is heated. These polymeric materials are converted to DL- α -lipoic acid in high yield when they are treated with dilute alkali (R. C. Thomas and L. J. Reed, *THIS JOURNAL*, **78**, 6148 (1956)).

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

Synthesis of DL-1,2-Dithiolane-3-caproic Acid and DL-1,2-Dithiolane-3-butyric Acid, Homologs of α -Lipoic Acid

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RECEIVED JUNE 29, 1956

DL-1,2-Dithiolane-3-caproic acid and DL-1,2-dithiolane-3-butyric acid have been synthesized. These homologs exhibited slight α -lipoic acid activity in the acetate-replacing factor assay.

It has been reported¹ that homologs of biotin are potent inhibitors of the utilization of this vitamin. Accordingly, the length of the valeric acid side chain in α -lipoic acid (1,2-dithiolane-3-valeric acid) was varied in an attempt to obtain metabolic antagonists of this biocatalyst. This paper describes a synthesis of DL-1,2-dithiolane-3-caproic acid (VIII) and DL-1,2-dithiolane-3-butyric acid (XII).

(1) M. W. Goldberg, L. H. Sternbach, S. Kaiser, S. D. Heineman, J. Scheiner and S. H. Rubin, *Arch. Biochem.*, **14**, 480 (1947).

These homologs exhibited, respectively, approximately 0.1 and 0.01% of the biological activity of DL- α -lipoic acid in the acetate-replacing factor assay.²

Ethyl 6,8-dichlorooctanoate (I)³ was reduced to 6,8-dichlorooctanol (II) with lithium aluminum

(2) B. M. Guirard, E. E. Snell and R. J. Williams, *ibid.*, **9**, 361 (1946); L. J. Reed, B. G. DeBusk, P. M. Johnston and M. E. Getzen-daner, *J. Biol. Chem.*, **192**, 851 (1951).

(3) L. J. Reed and C. I. Niu, *THIS JOURNAL*, **77**, 416 (1955).