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## Synthesis of DL-1,2-Dithiolane-3-butanesulfonamide, an Analog of $\alpha$ -Lipoic Acid

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pl-1,2-Dithiolane-3-butanesulfonamide has been synthesized. It was inactive as an antagonist of  $\alpha$ -lipoic acid in the acetate-replacing factor assay and in the enzymatic POF assay.

Although  $\alpha$ -lipoic acid (VIII) has been detected in a wide variety of organisms, only a few are known thus far which exhibit an absolute requirement for this biocatalyst.<sup>1</sup> The availability of antagonists of  $\alpha$ -lipoic acid could contribute to a further understanding of its metabolism, especially in those organisms which can synthesize  $\alpha$ -lipoic acid. Interest has developed, therefore, in the synthesis of compounds which might serve as metabolic antagonists of this substance.<sup>2</sup> This paper describes a synthesis of DL-1,2-dithiolane-3-butanesulfonamide (VII). This analog was inactive as an antagonist of  $\alpha$ -lipoic acid in the acetate-replacing factor assay,<sup>3</sup> employing a strain of Streptococcus lactis, and in the enzymatic POF assay.<sup>4</sup>



 $\mathbf{R} = \mathbf{CH}_2(\mathbf{Cl})\mathbf{CH}_2\mathbf{CH}(\mathbf{Cl})(\mathbf{CH}_2)_4 \mathbf{\overline{\phantom{a}}}$ 

Ethyl 6,8-dichloroöctanoate (I), an intermediate in a synthesis of  $DL-\alpha$ -lipoic acid,<sup>5</sup> was hydrolyzed with alcoholic potassium hydroxide and the dichloro acid produced was converted to the silver salt II. Treatment of the latter compound with bromine<sup>6</sup> gave 7-bromo-1,3-dichloroheptane (III). Compound III was converted to 5,7-dichloroheptyl thiolacetate (IV) by treatment with potassium thiolacetate in boiling ethanol.<sup>7</sup> Compound IV exhibited an absorption maximum at 232 m $\mu$ , which is characteristic of thiolesters.<sup>8</sup> The thiolacetate IV was treated with chlorine to produce the

(2) E. L. R. Stokstad, Federation Proc., 13, 712 (1954).

(3) B. M. Guirard, E. E. Snell and R. J. Williams, Arch. Biochem., 9, 361 (1946); L. J. Reed, B. G. DeBusk, P. M. Johnston and M. E. Getzendaner, J. Biol. Chem., 192, 851 (1951).

- (4) I. C. Gunsalus, M. I. Dolin and L. Struglia, ibid., 194, 849 (1952).
- (5) L. J. Reed and C-I. Niu, THIS JOURNAL, 77, 416 (1955).
- (6) H. Hunsdieker and C. Hunsdieker, Ber., 75, 291 (1942).
  (7) R. M. Evans and L. N. Owen, J. Chem. Soc., 244 (1949).
  (8) F. Lynen, Federation Proc., 12, 683 (1953).

sulfonyl chloride,9 which was converted to the sul-5,7-Dichloroheptanesulfonamide fonamide (V). (V) was allowed to react with sodium benzylmercaptide in boiling ethanol<sup>5</sup> to give 5,7-di-(benzylthio)-heptanesulfonamide (VI). The latter compound was reduced with sodium in liquid ammonia, and the dithiol produced was oxidized to DL-1,2-dithiolane-3-butanesulfonamide (VII). The cyclic disulfide VII was a yellow crystalline solid which exhibited the characteristic ultraviolet absorption spectrum of the 1,2-dithiolane moiety, with an absorption maximum at  $332 \text{ m}\mu$ .<sup>5,10</sup>

## Experimental<sup>11</sup>

Silver 6,8-Dichloroöctanoate (II).—A solution of 131 g. (0.54 mole) of ethyl 6,8-dichloroöctanoate<sup>5</sup>

and 72 g. (1.08 moles) of potassium hydroxide in 650 ml. of ethanol was allowed to stand at room temperature for 20 hours. The reaction mixture was poured into 31. of water and unchanged ester was removed by extraction with three 500-ml. portions of ether. The aqueous layer was acidified and the product extracted with ether. The ether extract was evaporated in vacuo and the oily residue was dissolved in 2 1. of water by the addition of approximately 550 ml. of 1 N sodium hydroxide. To the clear solution (pH 9) was added dropwise, with vigorous stirring, 550 ml. of 1 N silver nitrate. The precipitate was collected on a büchner funnel, washed successively with 10 1. of water and 21. of ethanol, and then dried in vacuo over phosphorus pentoxide. The yield of crude silver salt was 148 g. (85%).

7-Bromo-1,3-Dichloroheptane (III).--A solution of 74 g. (0.46 mole) of bromine in 630 ml. of carbon tetrachloride was pre-

pared from reagents which had been dried over phospho-rus pentoxide. This solution was stirred and maintained at 10° while 148 g. (0.46 mole) of silver 6,8-dichloroöctanoate was added in portions. When approximately one-quarter of the silver salt had been added, a vigorous evolution of carbon dioxide occurred. When the addition of silver salt was complete (1 hour) the reaction mixture was heated at 50° until evolution of carbon dioxide ceased (approximately 1 hour). The silver bromide was removed by filtration and the filtrate was washed with 5% sodium bisulfite solution to remove unchanged bromine. The organic layer was washed successively with 250 ml. of  $2\,N$  sodium hydroxide and 500 ml. of water, and then 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 col-lected, followed by the main fraction, 54 g. (58%), b.p. 103- $107^{\circ} (0.4 \text{ mm.}), n^{25} \text{D} 1.5008.$ 

Anal. Calcd. for C<sub>7</sub>H<sub>13</sub>BrCl<sub>2</sub>: C, 33.90; H, 5.28. Found: C, 33.72; H, 5.02.

(11) Boiling points and melting points are uncorrected.

<sup>(1)</sup> L. J. Reed, Physiol. Rev., 33, 544 (1953).

<sup>(9)</sup> I. B. Douglass and T. B. Johnson, THIS JOURNAL. 60, 1486 (1938).

<sup>(10)</sup> J. A. Barltrop, P. M. Hayes and M. Calvin, ibid., 76, 4348 (1954)

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 150ml. 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.);  $n^{25}$ D 1.5032;  $\lambda_{max}^{85\%}$  ethanol 232 mµ ( $\epsilon$  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  $C_7H_{18}Cl_2NO_2S$ : 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 benzeneSkellysolve B<sup>13</sup> to yield 3.51 g. (69%) of product. A sample was recrystallized for analysis, m.p.  $67.5-68^{\circ}$ .

Anal. Calcd. for  $C_{21}H_{29}NO_2S_3$ ; 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-butanesulfonamide (VII).--5.7-Di-(benzylthio)-heptanesulfonamide (3.0 g., 0.0069 mole) was reduced with sodium in liquid ammonia in a manner described previously.<sup>5</sup> 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). 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 ob-The polymeric material was warmed on a steamtained. bath with 20 ml. of 0.5 N sodium hydroxide until it dissolved (approximately 10 minutes). The resulting bright yellow solution<sup>18</sup> 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 re-moved *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°;  $\lambda_{\rm min}^{\rm 86\%}$  ethanol 332 m $\mu$  ( $\epsilon$  157),  $\lambda_{\rm min}$ 280 mµ.

Anal. Calcd. for  $C_7H_{15}NO_2S_8$ : 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.  $60-68\,^{\rm o},$  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-dithioloctanoic acid to the cyclic disulfide,  $DL-\alpha$ -lipoic acid (ref. 5), and also when the cyclic disulfide is heated. These polymeric materials are converted to  $DL-\alpha$ 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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## Synthesis of DL-1,2-Dithiolane-3-caproic Acid and DL-1,2-Dithiolane-3-butyric Acid, Homologs of $\alpha$ -Lipoic Acid

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

It has been reported<sup>1</sup> that homologs of biotin are potent inhibitors of the utilization of this vitamin. Accordingly, the length of the valeric acid side chain in  $\alpha$ -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- $\alpha$ -lipoic acid in the acetate-replacing factor assay.<sup>2</sup>

Ethyl 6,8-dichloroöctanoate (I)<sup>3</sup> was reduced to 6,8-dichloroöctanol (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. Getzendaner, J. Biol. Chem., 192, 851 (1951).

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