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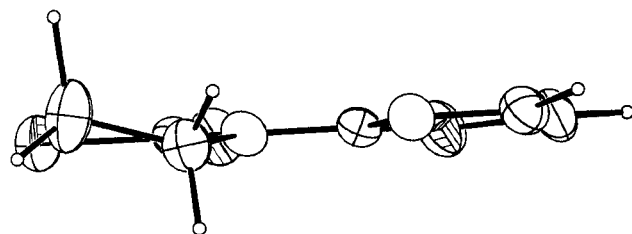
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A single crystalline enantiomer of 2-(2-thioxothiazolidin-3-yl)thiazole **5** has been isolated as the major product of the pyrolysis of 3-(2-thiazolin-2-yl)thiazolidine-2-thione **3** ( $n = 1$ ); the latter isolated as the sole product of the reaction between thiazolidine-2-thione **2** ( $n = 1$ ) and diethyl azodicarboxylate (DEAD) in benzene.

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### Introduction.

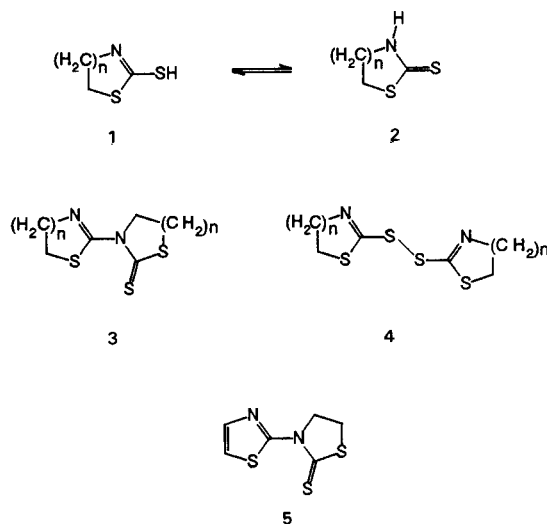
The gentle oxidation of thiols to disulfides has a long history [2] and the synthesis of these and related compounds with sulfur-sulfur bonds remains of interest because of the link between sulfane-sulfur containing organic species and cyanide detoxification [3]. Thus, challenged with cyanide, the liver enzyme rhodanese (thiosulfate sulfur transferase [E.C. 2.8.1.1]) [4] apparently undergoes sulfur-sulfur bond cleavage to produce thiocyanate, which is subsequently excreted. Since there is some evidence that other sulfur-sulfur bond cleavage reactions (*e.g.* in cystine) [5] are promoted by cyanide, we have undertaken a study of such processes [6] and have prepared, among others, the disulfide of 2-mercaptothiazoline, which we find undergoes rearrangement and dehydrogenation to the hitherto unknown 2-(2-thioxothiazolidin-3-yl)thiazole, **5**. The latter spontaneously crystallizes as a single *enantiomer*.



### Discussion.

Contrary to expectation, [2] it was found some years ago that gentle oxidation of the putative thiazolidine-2-thiol (**1**,  $n = 1$ ) with hydrogen peroxide yielded the corresponding 3-(2-thiazolin-2-yl)thiazolidine-2-thione (**3**,  $n = 1$ ) [7]. Although a reasonable pathway was proposed, Fujita, *et al.* [8], who were able to affect regioselective *N*-acylation and

S-alkylation of the corresponding anion of **1** ( $n = 1$ ), suggested that the spectra of **1** ( $n = 1$ ) under neutral conditions were more in accord with its formulation as the corresponding thiazolidine-2-thione (**2**,  $n = 1$ ). We have also observed that the commercially available 2-mercaptothiazoline, **1** ( $n = 1$ ) exists exclusively in its tautomeric form, *i.e.*, thiazolidine-2-thione (**2**,  $n = 1$ ) in deuteriochloroform as demonstrated by its  $^{14}\text{N}$  nmr spectrum where only one type of nitrogen (broad singlet,  $-220$  to  $-240$  ppm, lit  $-210$  to  $-270$  ppm [9]) corresponding to the thioamide is observed. It was already known [10], when Fujita, *et al.* [8] completed their work, that perhydrothiazine-2-thione (**2**,  $n = 2$ ) underwent oxidation (with iodine in chloroform/triethylamine) to the disulfide **4** ( $n = 2$ ). The latter (*i.e.* **4**,  $n = 2$ ) was reported to produce the corresponding thione **3** ( $n = 2$ ) in the presence of a trace of acid [10].



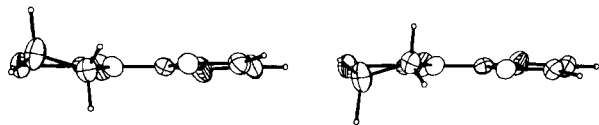
Among the more recent efforts in the synthesis and reactions of disulfides, and following the early results of Yoneda, *et al.* [11], Kato and Mitsunobu [12] demonstrated that thiols, both in the absence and presence of triphenylphosphine underwent reaction with diethyl azodicarboxylate (DEAD) to produce the corresponding disulfides and diethyl hydrazodicarboxylate.

Similarly, it had been early recognized by Mitsunobu, *et al.* [13] and subsequently acknowledged by others [14], that carbodiimides were readily produced from *N,N*-disubstituted thioureas on treatment with DEAD and triphenylphosphine in tetrahydrofuran (THF) and that thioamides yielded ketenimines under the same conditions. Perhaps less widely appreciated was the observation [13] that thioamides in the presence of sodium ethoxide in THF react with DEAD, nearly quantitatively, to yield the corresponding disulfides (*i.e.* **2** → **4**, *n* = 1).

We now report that, in the absence of base, 2-mercaptothiazoline (thiazolidine-2-thione, **2**, *n* = 1) reacts with DEAD to produce 3-(2-thiazolin-2-yl)thiazolidine-2-thione, **3** (*n* = 1) rather than the known [15] disulfide.

Routine mass spectrometric examination of the thiazolidine **3** (*n* = 1) suggested that thermal decomposition to the hitherto unknown 2-(2-thioxothiazolidin-3-yl)thiazole **5**, or a different dehydrogenation product was occurring (*i.e.*, loss of H<sub>2</sub> giving a parent ion M<sup>+</sup> at *m/z* = 204 as well as a large daughter at *m/z* = 202).

Pyrolysis of the thiazolidine **3** (*n* = 1) at atmospheric pressure in a Kugelrohr apparatus produced **5** along with thiazolidine-2-thione **2** (*n* = 1) and some recovered starting material **3** (*n* = 1). Crystallization of **5** from methanol, provided yellowish rhombic crystals, mp 121-122°, which, by X-ray crystallography [16], are composed of only one *enantiomer* (Figure) of the conformationally related pair that arise from the puckering of the thiazolidine ring. Presumably, lattice forces restrain interconversion.



The spontaneous resolution of the symmetrical, hitherto unreported 2-(2-thioxothiazolidin-3-yl)thiazole **5**, into one isomer (see Figure) is presumably of that special type of

Table 1. Bond Distances in Compound **5**, Å

S1-C1	1.732(6)	N1-C2	1.483(6)	C2-H2b	1.089(52)
S1-C3	1.806(6)	N1-C4	1.394(6)	C3-H3a	0.960(46)
S2-C1	1.645(5)	N2-C4	1.305(6)	C3-H3b	1.206(78)
S3-C4	1.716(5)	N2-C6	1.386(7)	C5-C6	1.339(8)
S3-C5	1.723(6)	C2-C3	1.473(9)	C5-H5	0.981(48)
N1-C1	1.359(6)	C2-H2a	0.921(67)	C6-H6	1.173(71)

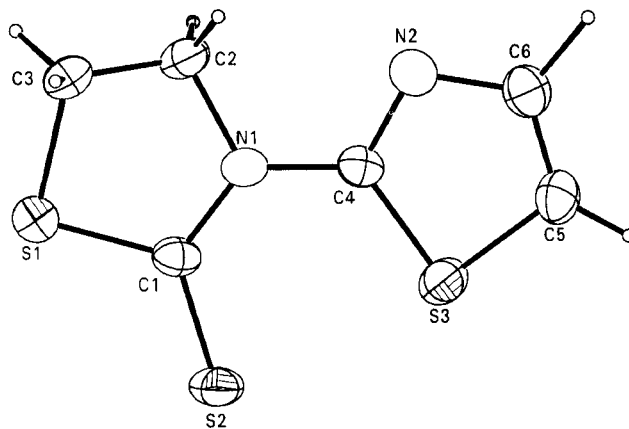
Table 2. Bond Angles in Compound **5**

C1-S1-C3	92.7(3)	N1-C2-H2a	107.9(47)	H3a-C3-H3b	113.0(47)
C4-S3-C5	88.5(3)	N1-C2-H2b	108.4(26)	S3-C4-N1	125.2(3)
C1-N1-C2	115.2(4)	C3-C2-H2a	103.9(54)	S3-C4-N2	115.6(4)
C1-N1-C4	126.7(4)	C3-C2-H2b	113.7(26)	N1-C4-N2	119.2(4)
C2-N1-C4	118.0(4)	H2a-C2-H2b	114.9(53)	S3-C5-C6	110.7(5)
C4-N2-C6	109.8(4)	S1-C3-C2	106.6(4)	S3-C5-H5	116.9(27)
S1-C1-S2	122.1(3)	S1-C3-H3a	105.7(21)	C6-C5-H5	132.4(27)
S1-C1-N1	111.3(3)	S1-C3-H3b	104.0(35)	N2-C6-C5	115.3(5)
S2-C1-N1	126.6(4)	C2-C3-H3a	115.0(27)	N2-C6-H6	115.2(46)
N1-C2-C3	107.7(4)	C2-C3-H3b	111.5(44)	C5-C6-H6	128.9(45)

process for which the term "second order" asymmetric transformation has been coined [17] and of which only a few other examples, *i.e.*, *N*-allyl-*N*-ethyl-*N*-methylanilinium iodide [18], tri-*o*-thymotide [19] and 1,1'-binaphthyl [20], have been documented.

## EXPERIMENTAL

Solvents were ACS Reagent Grade and were distilled before use. Melting points were obtained with a Thomas Hoover Capillary Melting Point Apparatus and are not corrected. The <sup>1</sup>H nmr and <sup>13</sup>C nmr spectra were obtained at 300 MHz and 75.47 MHz, respectively, on a GE 300 Omega spectrometer. The <sup>14</sup>N nmr spectra were obtained at 36.17 MHz on a GE 500 Omega spectrometer. Mass spectra were obtained on an Hp 5995 mass spectrometer. The ir spectra were obtained on a Mattson FT-IR 2020 spectrophotometer. Analyses were performed by Galbraith Laboratories, Knoxville, TN. The X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer employing graphite-monochromated Cu-K<sub>α</sub> radiation and using the ω-2θ scan technique.



3-(2-Thiazolin-2-yl)thiazolidine-2-thione (**3**, *n* = 1).

To a colorless solution of thiazolidine-2-thione (**2**, 5.0 g, 42 mmoles) in benzene (350 ml) was added (in the dark) diethyl azodicarboxylate (33.31 ml, 21 mmoles). The reaction mixture was stirred overnight at room temperature under an atmosphere of nitrogen. The yellowish heterogeneous reaction mixture was concentrated at reduced pressure and the residue taken up in a minimum of benzene and refrigerated at 5° until precipitation of

diethyl hydrazodicarboxylate was complete. The filtrate was concentrated and the residue, in methanol, deposited the title compound as yellow crystals which were recrystallized from the same solvent (3.57 g, 83%), mp 77-78°; ir (potassium bromide):  $\nu$  2939, 2852, 1581, 1388, 1315, 1285, 1254, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.72 (t, 2H,  $J = 7.8$  Hz,  $\text{H}_2\text{C}-\text{N}=\text{N}$ ), 4.01 (t, 2H,  $J = 8.3$  Hz,  $\text{H}_2\text{C}-\text{S}-\text{C}=\text{N}$ ), 3.41 (t, 2H,  $J = 7.8$  Hz,  $\text{H}_2\text{C}-\text{N}-\text{C}=\text{S}$ ), 3.32 (t, 2H,  $J = 8.3$  Hz,  $\text{H}_2\text{C}-\text{S}-\text{C}=\text{S}$ );  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  198.3 (C=S), 158.9 (C=N), 58.6 ( $\text{CH}_2-\text{N}=\text{N}$ ), 56.7 ( $\text{CH}_2-\text{N}-\text{C}=\text{S}$ ), 36.2 ( $\text{CH}_2-\text{S}-\text{C}=\text{N}$ ), 28.6 ( $\text{CH}_2-\text{S}-\text{C}=\text{S}$ );  $^{14}\text{N}$  nmr (relative to  $\text{CH}_3\text{NO}_2$ , deuteriochloroform):  $\delta$  -106.2 (N=C), -206.5 (N-C=S); ms:  $m/z$  204 (molecular ion).

*Anal.* Calcd. for  $\text{C}_6\text{H}_8\text{N}_2\text{S}_3$ : C, 35.27; H, 3.95; N, 13.71. Found: C, 35.24; H, 3.90; N, 13.71.

#### 2-Mercaptothiazoline Disulfide (**4**, $n = 1$ ).

To a stirred solution of diethyl azodicarboxylate (DEAD, 1.66 ml, 10.5 mmoles) in chloroform (25 ml) under an atmosphere of nitrogen at room temperature and in the dark, there was added a solution of thiazolidine-2-thione (**2**, 2.5 g, 21 mmoles) in chloroform (125 ml) which also contained a trace of freshly prepared sodium methoxide in methanol (10 drops of a *ca.* 1 *M* solution added immediately before the two chloroform solutions were to be mixed). After stirring overnight, the solution was concentrated at reduced pressure and the yellowish residue taken up in a minimum amount of benzene. The precipitated diethylhydrazodicarboxylate (1.68 g) was removed by vacuum filtration and the filtrate concentrated at reduced pressure to a yellow oil which spontaneously crystallized. Recrystallization of the crude product from ether yielded the title disulfide as yellow needles, 1.32 g (53%), mp 76-77° (lit [15] 76-78°). On standing in the solid state as well as in solution this material slowly converted to 3-(2-thiazolin-2-yl)thiazolidine-2-thione (**3**,  $n = 1$ ) with extrusion of sulfur; ir (potassium bromide):  $\nu$  3123, 1936, 1855, 1672, 1445, 1304, 988, 920  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (acetone- $d_6$ ):  $\delta$  4.37 (t, 2H,  $J = 8.2$  Hz,  $\text{H}_2\text{C}-\text{N}=\text{N}$ ), 3.48 (t, 2H,  $J = 8.2$  Hz,  $\text{H}_2\text{C}-\text{S}-\text{C}=\text{S}$ );  $^{13}\text{C}$  nmr (acetone- $d_6$ ):  $\delta$  167.1 (C=N), 67.1 ( $\text{CH}_2-\text{N}=\text{N}$ ), 35.0 ( $\text{CH}_2-\text{S}-$ ).

#### 2-(2-Thioxothiazolidin-3-yl)thiazole (**5**).

3-(2-Thiazolin-2-yl)thiazolidine-2-thione (**3**, 300 mg, 1.5 mmoles) in a Kugelrohr tube was pyrolyzed at 250°. The distillate was washed from the tube with separate chloroform and methanol rinses which were subsequently combined and evaporated to yield 111 mg (37% weight recovery) of a dark-red oil. Preparative tlc (silica gel, 20 x 20 cm, 100  $\mu$ ) using ether as the eluant produced the title compound **5** ( $R_f = 0.84$ , 25 mg) along with recovered starting material **3** ( $R_f = 0.41$ , 15 mg) and thiazolidine-2-thione (**2**,  $R_f = 0.66$ , 42 mg). A second chromatography of 2-(2-thioxothiazolidin-3-yl)thiazole under the same conditions yielded 15.0 mg (5%) of a light yellow oil which crystallized from methanol to give yellowish rhombic crystals, mp 121-122°; ir (potassium bromide):  $\nu$  3106, 3065, 3000, 2946, 2893, 1490, 1469, 1441, 1386, 1325, 1301, 1283, 1252, 1168  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  7.60 (d, 1H,  $J = 3.5$  Hz,  $=\text{N}-\text{CH}=\text{C}$ ), 7.10 (d, 1H,  $J = 3.5$  Hz,  $=\text{CH}-\text{S}$ ), 5.1 (t, 2H,  $J = 7.8$  Hz,  $\text{CH}_2-\text{N}-\text{C}=\text{S}$ ), 3.6 (t, 2H,  $J = 7.8$  Hz,  $-\text{CH}_2-\text{S}-\text{C}=\text{S}$ );  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  193.8 (C=S), 158.8 (C=N), 136.9 (N-CH=), 114.5 (S-CH=), 58.4 ( $\text{CH}_2-\text{N}-\text{C}=\text{S}$ ), 28.4 ( $\text{CH}_2-\text{S}-\text{C}=\text{S}$ ); ms:  $m/z$  202 (molecular ion).

*Anal.* Calcd. for  $\text{C}_6\text{H}_6\text{N}_2\text{S}_3$ : C, 35.62; H, 2.99; N, 13.85. Found: C, 35.45; H, 2.98; N, 13.52.

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