

temperature for 36 hr, an additional 400 ml of methylene chloride was added, and the mixture was washed with water. Much of the product was insoluble in the organic layer and was collected on a filter (34 g). An additional 18 g of crystalline product was obtained by evaporation of the methylene chloride filtrate. The combined crude product (52 g, 95%) was dried and recrystallized from a mixture of benzene and petroleum ether to give colorless crystals: mp 133–133.5° dec; nmr (CDCl<sub>3</sub>) δ 2.15 (s, 3, CH<sub>3</sub>), 3.17–3.73 (m, 8, morpholine ring protons), 7.87 (s, 4, aromatic protons), 10.25 (m, 1, NH).

*Anal.* Calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: C, 45.55; H, 5.10; N, 8.86; S, 20.27. Found: C, 45.61; H, 5.11; N, 8.90; S, 20.35.

**Reaction of Morpholine with 4-(*p*-Acetamidophenylsulfonylthio)morpholine (2c).**—Morpholine (2.75 g, 0.0316 mol) was added to a suspension of 5.00 g (0.0158 mol) of 4-(*p*-acetamidophenylsulfonylthio)morpholine in 100 ml of carbon tetrachloride, and the mixture was stirred at ambient temperature for 17 hr. The precipitated morpholinium *p*-acetamidobenzenesulfinate was collected on a filter, washed with carbon tetrachloride, and dried. The salt, obtained in quantitative yield (4.5 g), was recrystallized from 2-propanol to give colorless crystals, mp 171.5–172.5°.

*Anal.* Calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: C, 50.33; H, 6.34; N, 9.79; S, 11.20. Found: C, 50.03; H, 6.28; N, 9.66; S, 11.23.

The carbon tetrachloride filtrate was concentrated *in vacuo*, leaving 3.0 g (94%) of crystalline 4-morphinosulfide, mp 123.5–124.5°. Recrystallization from ethanol gave the pure substance, mp 124.5–125.5° (lit.<sup>8</sup> mp 125–126°).

*Anal.* Calcd for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S: C, 47.03; H, 7.90; N, 13.72; S, 15.70. Found: C, 47.05; H, 7.87; N, 13.67; S, 15.72.

**Registry No.**—2a, 34764-81-3; 2b, 34764-82-4; 2c, 34764-83-5; 3, 5038-11-9; 4, 23837-27-6.

(8) E. S. Blake, *J. Amer. Chem. Soc.*, **65**, 1267 (1943).

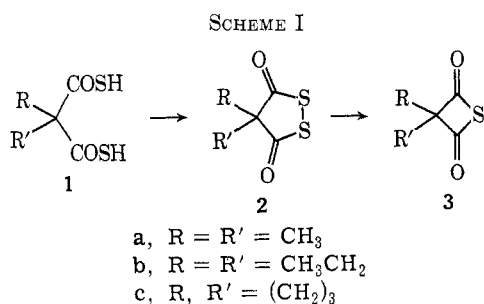
### Synthesis of 1,2-Dithiolane-3,5-diones and Thietane-2,4-diones<sup>1a</sup>

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Although 1,2-dioxolane-3,5-diones (malonyl peroxides)<sup>2</sup> and oxetane-2,4-diones (malonic anhydrides)<sup>3</sup> are known, the sulfur analogs have not been reported. Herein we describe a simple sequence for obtaining dialkylated 1,2-dithiolane-3,5-diones and thietane-2,4-diones *via* the pyridinium salts of the corresponding bisthio acids (1) (Scheme I).



Although bisthiomalonic acid has been reported to result by reaction of malonyl chloride with hydrogen

(1) (a) Presented at the 7th Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1972. (b) NDEA Fellow, 1968–1971.

(2) W. Adam and R. Rucktaschel, *J. Amer. Chem. Soc.*, **93**, 557 (1971).

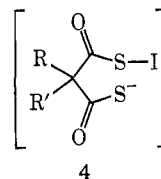
(3) A. C. Duckworth, *J. Org. Chem.*, **27**, 3146 (1962).

sulfide in pyridine solution, followed by acidification of the reaction mixture,<sup>4</sup> we were unable to effect this preparation. Parallel attempts to prepare the bisthio acids (or the intermediate pyridinium salts) from monoalkylmalonyl chlorides also failed.<sup>5</sup> However, reaction of disubstituted malonyl chlorides under similar conditions afforded the bisthio acids 1a–c as low-melting solids.

Since it is well documented that salts of monothio-carboxylic acids undergo oxidation with halogens to give diacyl disulfides,<sup>6</sup> it was anticipated that formation of 1,2-dithiolane-3,5-diones could be carried out analogously by oxidation of salts of the bisthiomalonic acids (1). Reconversion of the thio acids to their pyridinium salts,<sup>7</sup> followed by oxidation with iodine in anhydrous ether solution,<sup>8</sup> gave the cyclic disulfides 2a–c in 55–80% yields, accompanied by small amounts (5%) of the corresponding thietane-2,4-diones 3a–c. The thietanes were observed by gc, ir, and nmr analysis on the crude reaction mixtures and were identified by comparison with data obtained on pure samples obtained by alternate procedures (*vide infra*).

The ir spectra for the 1,2-dithiolane-3,5-diones 2a–c exhibit strong absorptions at approximately 1720 and 1680 cm<sup>-1</sup>, apparently as a result of vibrational coupling for the diacyl disulfide group. The structures for 2a–c are further supported by elemental analysis and nmr and mass spectral data.

Oxidation of the salts of the bisthiomalonic acids with iodine presumably involves formation of intermediate sulfonyl iodides of type 4,<sup>9</sup> which undergo



intramolecular displacement of iodide by thiocarboxylate ion to provide the expected 1,2-dithiolane-3,5-diones. The unexpected formation of thietane-2,4-diones 3a–c appears to be the result of intramolecular displacement of the –SI group from the sulfonyl iodide intermediate. The possibility that 3a–c might result from overoxidation of the disulfides was ruled out by subjecting 2a to the conditions of the oxidation.

Reaction of the cyclic disulfides 2a–c with triphenylphosphine in benzene at 60° gave the colorless, distillable thietanes 3a–c in high yields.<sup>10</sup> The ir spectra of 3a–c exhibit bands at 1850 and 1750 cm<sup>-1</sup> which are attributed to vibrational coupling of the thioanhydride function.

(4) S. Sunner, *Svensk Kem. Tidskr.*, **62**, 204 (1950).

(5) Considering the ease with which the acid chlorides undergo elimination in basic media [M. Rabjohn and H. M. Molotsky, *J. Org. Chem.*, **23**, 1642 (1958)], these results are not too surprising.

(6) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 4, Chemical Publishing Co., New York, N. Y., 1962, p 22.

(7) Isolation of the free thioacids was carried out in order to obtain pure pyridinium salts.

(8) It was necessary to run these reactions in a nonnucleophilic medium in order to avoid solvolysis of the disulfides.

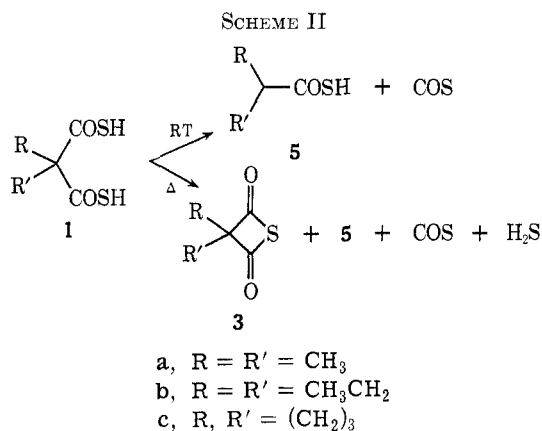
(9) J. P. Danehy, C. P. Egan, and J. Switalski, *J. Org. Chem.*, **36**, 2530 (1971), have demonstrated the intermediacy of sulfonyl iodides during the oxidation of thiols.

(10) D. N. Harpp and J. G. Gleason, *J. Amer. Chem. Soc.*, **93**, 2437 (1971), have described the desulfurization of 1,2-dithiolanes to thietanes by treatment with tris(diethylamino)phosphine.

Extensive fragmentation of **3a-c** to carbonyl sulfide and the corresponding ketenes occurred during gc analysis employing inlet port temperatures above 150°. Samples of the peaks assigned as ketenes were collected and found to possess the characteristic ketene ir absorptions at 2100 cm<sup>-1</sup>. Thermal decomposition of a neat sample of diethylthietane-2,4-dione (**3b**) in a microdistillation apparatus provided diethylketene in high yield. Similar treatment of dimethylthietane-2,4-dione (**3a**) by heating in an unsealed tube gave the dimethylketene dimer, 2,2,4,4-tetramethylcyclobutane-1,3-dione.<sup>11</sup>

The thietane **3a** was also obtained in high yield by treatment of the pyridinium salt of the bithio acid **1a** with trifluoroacetic anhydride at room temperature.

Although the bithio acids **3a-c** are stable in the solid state at -15°, ir and nmr studies indicate that the neat liquids undergo facile loss of carbonyl sulfide at room temperature to yield monothio acids<sup>12</sup> (Scheme II).



At temperatures above 80° formation of thietane-2,4-diones **3** by loss of hydrogen sulfide is also observed.<sup>13</sup>

#### Experimental Section<sup>14</sup>

**Preparation of the Bithiomalonic Acids 1a-c.**—In a 250-ml round-bottom flask equipped with gas inlet and outlet tubes, pressure-equalizing funnel, ice bath, and magnetic stirrer was placed 36 g of anhydrous pyridine. The pyridine was saturated with hydrogen sulfide for 30 min; then a solution of 0.05 mol of the appropriate disubstituted malonyl chloride in 20 ml of anhydrous ether was added *via* the dropping funnel over a period of 2-3 hr (bath temperature 0-10°). Hydrogen sulfide addition was continued during addition of the malonyl chloride. The reaction mixture was then poured into a mixture of 400 g of cracked ice and 20 ml of concentrated H<sub>2</sub>SO<sub>4</sub> and extracted with three 75-ml portions of ether. The combined extract was washed with ice water, dried (MgSO<sub>4</sub>), and evaporated *in vacuo* to provide the

(11) By analogy, oxetane-2,4-diones undergo thermal decomposition to give carbon dioxide and ketenes (ref 2). I. L. Knunyants and O. V. Kil'disheva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 619 (1955), have reported the thermal cleavage of a substituted 2-thietanone to give carbonyl sulfide and the corresponding olefin.

(12) In contrast, 1,1-dicarboxylic acids undergo decarboxylation only at temperatures well above 100°: P. I. Abell and R. Tien, *J. Org. Chem.*, **30**, 4212 (1965).

(13) By comparison, bithiosuccinic and bithio-*o*-phthalic acids are not isolable, but undergo rapid loss of hydrogen sulfide to form the cyclic thioanhydrides (ref 6, p 21).

(14) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Mass spectra were obtained through Schrader Analytical Laboratories, Detroit, Mich. Ir spectra were obtained on a Perkin-Elmer Model 337 instrument. Nmr spectra were determined with a Varian A-60 instrument. Glpc was carried out on a Hewlett-Packard F & M Model 700 instrument, employing a 6 ft × 0.25 in. stainless steel column packed with 10% SE-30 on silanized 60-80 mesh Chromosorb W.

liquid bithio acids, which solidified to white solids at 20-25°. The bithio acids were not further purified due to their lability at room temperature. The ir and nmr spectra of these compounds (Table I) verified the assigned structures.

TABLE I  
PHYSICAL DATA<sup>d</sup>

Compd	Bp, °C (mm)	Yield, %	Ir, <sup>a</sup> cm <sup>-1</sup>	Nmr <sup>b</sup>	
<b>1a</b>	c	50	2600, 1680	1.55 (s, 6 H)	4.70 (s, 2 H)
<b>1b</b>	c	70	2600, 1680	0.9 (t, 6 H)	1.90 (q, 4 H)
				5.0 (s, 2 H)	
<b>1c</b>	c	83	2600, 1680	1.95 (m, 2 H)	2.6 (m, 4 H)
				4.8 (s, 2 H)	
<b>2a</b>	80-82 (5)	57	1720, 1680	1.42 (s, 6 H)	
<b>2b</b>	47-48 (0.5)	80	1720, 1680	0.93 (t, 6 H)	1.90 (q, 4 H)
<b>2c</b>	67-69 (0.1)	82	1760, 1670	2.5 (m, 6 H)	
<b>3a<sup>e</sup></b>	50-51 (15)	86	1850, 1760	1.53 (s, 6 H)	
<b>3b<sup>e</sup></b>	32-34 (0.1)	83	1840, 1740	1.15 (t, 6 H)	1.76 (q, 4 H)
<b>3c<sup>e</sup></b>	39-41 (0.5)	87	1850, 1750	2.02 (m, 2 H)	2.74 (m, 4 H)

<sup>a</sup> Liquid films. <sup>b</sup> CCl<sub>4</sub> solutions, employing TMS as the internal reference. <sup>c</sup> Unstable liquid, mp 20-25°. <sup>d</sup> Satisfactory analyses (±0.25% for C, H, and S) were reported for compounds **2a-c** and **3a-c**: Ed. Nominal molecular weights were determined by mass spectrometry; isotopic abundance of P + 1 and P + 2 peaks were as expected. <sup>e</sup> The mass spectrum indicated COS and the ketene as the principal fragments, due at least in large part to thermal cleavage.

**Thermal Decomposition of the Bithio Acids.**—Ir and nmr analysis of a sample of **1a** which had been stored at -15° for 18 months showed 5-8% decomposition to thioisobutyric acid; however, when a neat sample of **1a** was allowed to stand at 26° for 22 hr, spectral analysis indicated 95% decomposition to thioisobutyric acid. The formation of thioisobutyric acid was verified by comparison of the ir and nmr spectra with those obtained on a sample prepared from isobutyryl chloride and H<sub>2</sub>S.<sup>15</sup> Gc analysis of **1a** at 280° inlet port temperature resulted in extensive decomposition to thioisobutyric acid, COS, and H<sub>2</sub>S accompanied by thietane-2,4-dione (**3a**) in 15-20% yield. Gc analysis at 80° resulted in the formation of only thioisobutyric acid and COS.

The thermal instability of **2a** and **3a** qualitatively paralleled that observed for **1a**.

**Preparation of the 1,2-Dithiolane-3,4-diones 2a-c.**—To a solution of 0.025 mol of the appropriate bithiomalonic acid in 300 ml of anhydrous ether was added 3.96 g (0.05 mol) of pyridine. The mixture was titrated with 1.5 M iodine in ether until the color of iodine just persisted. The reaction mixture was filtered and the filtrate was washed successively with 10-ml portions of 0.1 N Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, 10% HCl, and 10% Na<sub>2</sub>CO<sub>3</sub> solution. The ether extract was then dried (MgSO<sub>4</sub>) and evaporated at 100 mm pressure, and the residue was distilled *in vacuo*. The physical and analytical data obtained for **2a-c** are listed in Table I.

Distilled samples of **2a-c** prepared by the above procedure contained 1% of the corresponding thietanes **3a-c** which were detected by gc and spectral analysis. Examination of crude samples of **2a** before aqueous work-up and distillation indicated the presence of 4% of **2a**. When a sample of 99% pure **2a** was subjected to the conditions of the oxidation (2 mmol of pyridine, 1 mmol of pyridinium iodide, and 1 mmol of iodine per mmol of **2a** in ether solution) only a trace of the thietane **3a** could be detected in the crude product.

**Preparation of the Thietane-2,4-diones 3a-c. A. Reaction of 1,2-Dithiolane-3,5-diones 2a-c with Triphenylphosphine.**—In a 25-ml round-bottom flask fitted with a reflux condenser and Drierite drying tube was placed a solution of the appropriate cyclic disulfide (**2a-c**) in 10 ml of benzene. The solution was stirred at 60° and 5.25 g (0.02 mol) of triphenylphosphine was added in small portions over a period of 8 hr. After removal of the triphenylphosphine sulfide by filtration, the filtrate was evaporated at 100 mm pressure and the residue was distilled to provide the desired thietane-2,4-dione. The physical and analytical data for **3a-c** are shown in Table I.

**B. Reaction of Dimethylbithiomalonic Acid (1a) with Trifluoroacetic Anhydride.**—To a stirred solution of 5.1 g (0.031 mol) of trifluoroacetic anhydride was added 6.1 g (0.031 mol) of dimethylbithiomalonic acid in 10 ml of anhydrous ether. The mixture was allowed to stand for 10 min, and then was diluted to

(15) Reference 6, p 61.

160 ml with petroleum ether (bp 30–60°) and 5.2 g (0.066 mol) of pyridine was added with stirring. The reaction mixture was then filtered to remove pyridinium salts and the filtrate was evaporated at 100-mm pressure to give 3.7 g (95% yield) of **3a**.

**Thermolysis of 3a and 3b.**—A neat sample of 3,3-dimethylthietane-2,4-dione (**3a**) was heated at 145° for 1.5 hr (evolution of gas began at 130°). On cooling, a white, crystalline solid formed. A sample sublimed at atmospheric pressure gave mp 113–115°. The melting point was not depressed upon admixture with 2,2,4,4-tetramethylcyclobutane-1,4-dione (obtained from Aldrich Chemical Co). Nmr (singlet at 1.31 ppm) confirmed the identity.

A neat sample of 3,3-diethylthietane-2,4-dione (**3b**) was placed in a short-path microdistillation apparatus equipped with a Dry Ice cooled receiver and heated under nitrogen, at atmospheric pressure from room temperature to 170° over a 30-min period. Gas evolution was apparent at 145°. The ir spectrum of the pale yellow liquid which distilled into the receiver showed a strong band at 2100  $\text{cm}^{-1}$  (diethylketene<sup>3</sup>) and a weak absorption for starting material at 1820  $\text{cm}^{-1}$ . Gc analysis indicated the presence of 95% diethylketene and 5% starting material.

**Registry No.**—**1a**, 34803-94-6; **1b**, 34803-95-7; **1c**, 34803-96-8; **2a**, 34803-97-9; **2b**, 34803-98-0; **2c**, 34803-99-1; **3a**, 34804-00-7; **3b**, 34804-01-8; **3c**, 34804-02-9.

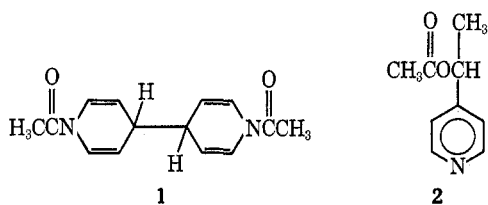
### Zinc Reduction of 4-Methylpyridine in Acetic Anhydride

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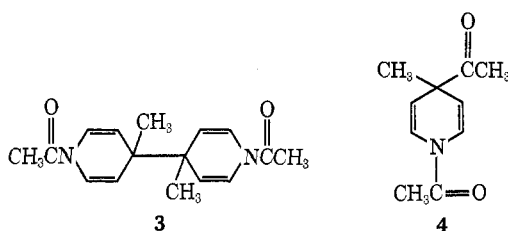
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Mild treatment of pyridine with zinc and acetic anhydride results in the formation of 1,1'-diacetyl-1,1',4,4'-tetrahydrobipyridine (**1**).<sup>1,2</sup> Pyrolysis of **1** at



2 mm and 250–275° results in the formation of 1-(4-pyridyl)ethyl acetate<sup>3</sup> (**2**).

The present work is an attempt to prepare 1,1'-diacetyl-4,4'-dimethyl-1,1',4,4'-tetrahydrodipyridine (**3**)



by applying the conditions of the zinc reduction to 4-methylpyridine. We did not obtain the expected prod-

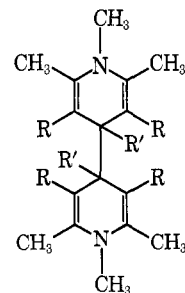
uct **3**, but instead we obtained 1,4-diacetyl-4-methyl-1,4-dihydropyridine (**4**).

The zinc reduction product of 4-methylpyridine and acetic anhydride was shown not to be structure **3** on the basis of molecular weight and elemental analysis. The assignment of **4** as the structure is based upon the nmr spectrum. Low-field protons assigned to H<sub>2</sub> and H<sub>6</sub> occur as a double doublet at  $\delta$  7.28 and 6.77 ( $J = 7.5$  cps) with an area of 1 for each doublet. H<sub>3</sub> and H<sub>5</sub> occur as a single doublet at  $\delta$  4.97 ( $J = 7.5$  cps), with an area of 2. Two methyl signals (area of 3) occur as sharp singlets at  $\delta$  2.27 and 2.22 and are assigned as the acetyl signals. A third methyl (area of 3) occurs as a singlet at  $\delta$  1.27 and is assigned as the 4-methyl group of **4**. The nmr spectrum of **4** in CDCl<sub>3</sub> is very similar to that of **1** in CDCl<sub>3</sub>, in which the 2,2' and 6,6' protons occur as a double doublet at  $\delta$  7.23 and 6.68 with coupling constant of 11 cps, and the 3,3',5,5' protons of **1** occur as a multiplet at  $\delta$  4.92.<sup>4</sup> Due to their *N*-acetyl groups the nmr absorptions of the ring protons of **1** and **4** occur at much lower field than the corresponding absorptions of other dihydropyridines. Examples are the chemical shifts for 1-phenyl-1,4-dihydropyridine<sup>5</sup> and 1,4,4-trimethyl-1,4-dihydropyridine,<sup>6</sup> which occur at  $\delta$  6.27 and 5.51 for the 2,6 protons and at  $\delta$  4.53 and 4.11 for the 3,5 protons.

The infrared spectrum of **4** displays very strong bands at 1670 and 1692  $\text{cm}^{-1}$ . The 1670- $\text{cm}^{-1}$  band is attributed to the  $>\text{C}=\text{C}<$  by analogy with other dihydropyridine systems.<sup>3,6,7</sup> The 1692 and 1624- $\text{cm}^{-1}$  bands are due to carbonyl stretching of **4** and **1**.

The ultraviolet spectrum of **4** in water, 1 *M* HCl, 0.1 *M* HCl, and 0.1 *M* NaOH occurs at 2530 Å with an extinction coefficient of  $1.9 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ . An overnight treatment of **4** with 0.1–1 *M* HCl or 0.1–1 *M* NaOH completely abolishes its ultraviolet absorbance, indicating hydrolytic instability of **4**. The ultraviolet absorbance of **4** is similar to that of **1**<sup>4</sup> ( $\lambda_{\text{max}}$  2630 Å,  $\epsilon_{\text{max}}$   $2.4 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ ).

The failure to obtain **3** upon treatment with zinc and acetic anhydride can be ascribed to the instability of bipyridines which are hindered at the 4,4' positions. The early work of Mumm<sup>8,9</sup> and Emmert<sup>10</sup> clearly indicates that compounds **5–7**, formed by reduction of



- 5**, R = CO<sub>2</sub>Et; R' = *i*-Bu  
**6**, R = R' = CH<sub>3</sub>  
**7**, R = H; R' = CH<sub>3</sub>

(4) A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *ibid.*, **29**, 2175 (1964).

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