corresponding carboxamide. This was unsuccessful; the only product, isolated in low yield, was **17**: mp 130–131°; mass spectrum (70 eV) *m/e* (rel intensity) 273 (100), 159 (71), 114 (15), 81 (25).

Anal. Calcd for $C_{15}H_{15}NS_2$: C, 65.89; H, 5.53; N, 5.12; S, 23.46. Found: C, 65.75; H, 5.53; N, 5.27; S, 23.47.

Reactions of 9a with Electrophiles. 2,4-Dinitrobenzenesulfenyl Chloride.—The sulfenyl chloride (469 mg, 2 mmol) was allowed to react with 348 mg (2 mmol) of **9a** in 5 ml of methylene chloride for 0.5 hr, sodium carbonate was added, and the solution was filtered and evaporated to leave a red syrup which was chromatographed on alumina. Elution with 1:1 methylene chloride-hexane yielded 379 mg (51%) of 2-[α-(2,4-dinitrophenylthio)butylidene]-1,3-dithiane as a red syrup which crystallized on standing: nmr ($CDCl_3$) δ 7.4–9.1 (ABM pattern, 3, J = 9 and 3 Hz, aromatic), 3.1 (q, 4, SCH_2), 2.8–1.2 (m, 6, ring and propyl methylenes), 0.9 (5, 3, CH_3–).

Recrystallization from ethanol gave the analytical sample, mp 99–100°.

Anal. Calcd for $C_{14}H_{16}N_2O_4S_3$: C, 45.14; H, 4.33; N, 7.52; S, 25.83. Found: C, 45.10; H, 4.50; N, 7.35; S, 25.66.

***p*-Nitrobenzenediazonium Fluoroborate.**—In 20 ml of methylene chloride was dissolved 1.0 g (5.75 mmol) of **9a**, and 1.365 g (5.75 mmol) of *p*-nitrobenzenediazonium fluoroborate was added. After 1 hr 400 ml of water was added, the layers were separated, and the water layer was extracted with four 50-ml portions of methylene chloride. After drying (Na_2SO_4) and evaporating the methylene chloride, 1.57 g (85%) of 2-[α-(*p*-nitrophenylazo)-butylidene]-1,3-dithiane was obtained. Recrystallization from ethanol gave purple needles, mp 107.5–108.5°.

Anal. Calcd for $C_{14}H_{17}N_3O_2S_2$: C, 51.99; H, 5.30; N, 12.99; S, 19.83. Found: C, 51.86; H, 5.40; N, 13.01; S, 19.75.

Tri-*n*-butyltin Hydride Reduction of 15a.—A solution containing 145.7 mg (0.5 mmol) of tri-*n*-butyltin hydride and 163.6 mg (0.5 mmol) of **15a** in toluene was refluxed under N_2 overnight and evaporated, and the residue was taken up in methanol to deposit 70.2 mg (56%) of yellow crystals, mp 86–89°, which were identified as **6** by ir.

Registry No.—**6**, 30765-32-3; **9a**, 17590-62-4; **9c**, 12526-80-6; **13a**, 21792-53-0; **13b**, 30765-35-6; **13c**, 12526-81-7; **15a**, 30908-67-9; **15b**, 30765-36-7; **15c**, 30765-37-8; **15d**, 30765-38-9; **15e**, 30765-39-0; **15f**, 30765-40-3; **15g**, 30765-42-5; **17**, 30765-41-4; 2-[α-(2,4-dinitrophenylthio)butylidene]-1,3-dithiane, 30765-43-6; 2-[α-(*p*-nitrophenylazo)butylidene]-1,3-dithiane, 30765-44-7.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Organic Disulfides and Related Substances. 32. Preparation and Decomposition of β-Substituted Ethyl Acetyl Disulfides[1a–c]

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Of seven approaches for the synthesis of β-substituted ethyl acetyl disulfides, $AcSS(CH_2)_2X$, the most promising was based on a procedure of Böhme and Clement that involves reaction of acetylsulfenyl chloride with a thiol. Evidence for the structure of typical products was based on ir, nmr, and mass spectra, and on independent synthesis. The order of increasing resistance to decomposition (and hence of decreasing effect of a functional group X) was $NH_3^+ \sim NH^+{}_2\text{-}n\text{-}C_{10}H_{21} < NHAc < CO_2H \sim CO_2Me < Cl \sim {=}CH_2 \sim CH_3$. This order is attributed to diminishing assistance by X in the cleavage of the acetyl–sulfur and/or the sulfur–sulfur bond. Of the compounds tested, only three showed significant *in vitro* activity against *Histoplasma capsulatum*.

Previous reports have described the disproportionation of unsymmetrical disulfides containing 2-aminoethyl and derivative moieties.[2] The possibility of anchimeric assistance to disproportionation by the amine function was first suggested for benzyl 2-(*n*-decylamino)ethyl disulfides.[2f] Recently, studies of disulfides containing an *o*-carboxyphenyl moiety strongly suggested that the *o*-carboxylate function also can anchimerically assist disproportionation,[1a] and studies of methyl and 2-acetamidoethyl acetyl disulfide suggested that the amide group likewise accelerates decomposition.[3]

(1) (a) Paper 31: L. Field, P. M. Giles, Jr., and D. L. Tuleen, *J. Org. Chem.*, **36**, 623 (1971). (b) This investigation was supported by Public Health Service Research Grants No. AM11685 from the National Institute of Arthritis and Metabolic Diseases (L. F.) and AI-08916 from the National Institute of Allergy and Infectious Diseases (I. McV.). (c) Taken from part of the Ph.D. dissertation of W. S. H., which may be consulted for further details (Vanderbilt University, Jan 1971). (d) Department of Chemistry. (e) Department of General Biology.

(2) (a) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961); (b) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964); (c) R. R. Crenshaw and L. Field, *ibid.*, **30**, 175 (1965); (d) L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966); (e) L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966); (f) M. Bellas, D. L. Tuleen, and L. Field, *ibid.*, **32**, 2591 (1967); (g) L. Field and J. D. Buckman, *ibid.*, **32**, 3467 (1967); (h) L. Field, H. K. Kim, and M. Bellas, *J. Med. Chem.*, **10**, 1166 (1967); (i) L. Field and J. D. Buckman, *J. Org. Chem.*, **33**, 3865 (1968); (j) L. Field and R. B. Barbee, *ibid.*, **34**, 1792 (1969).

(3) L. Field, W. S. Hanley, I. McVeigh, and Z. Evans, *J. Med. Chem.*, **14**, 202 (1971).

The preparation and investigation of β-substituted ethyl acetyl disulfides, *i.e.*, of $AcSS(CH_2)_2X$, had a twofold purpose: (a) to clarify the importance of functional group assistance to acetyl–sulfur and/or sulfur–sulfur cleavage with β-substituted disulfides and to compare the relative effectiveness of functional groups; and (b) to determine whether these functional groups would lead to a greater inhibitory effect than was found for methyl acetyl disulfide on *H. capsulatum*, a fungal pathogen for man.[3]

Seven possible approaches were compared in preparing the acetyl disulfides **1–11** shown in Table I. The sulfenyl chloride method of eq 1, employed in the preparation of unfunctionalized carbonyl disulfides,[3] was

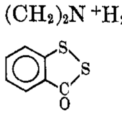
$$RSH \xrightarrow{0.5Cl_2} 0.5(RS)_2 \xrightarrow{0.5Cl_2} RSCl \xrightarrow{AcSH} AcSSR + HCl \quad (1)$$

unpromising except for the preparation of **1** and **11**. Insolubility of the symmetrical disulfides in CH_2Cl_2 precluded the formation of sulfenyl chlorides necessary for the preparation of compounds **2**, **3**, **5**, and **9** Allyl mercaptan (for **6**) and α-mercaptoacetone did not give sulfenyl chlorides on treatment with chlorine, not unexpectedly, but gave other undetermined reaction products.

A method of Hiskey and coworkers was tried briefly

Table I

Synthesis of Substituted Carbonyl Disulfides: AcSX + RSY → AcSSR + XY[a]

Compd	AcSSR, R	Method	Product: Yield,[b] %	Product: Bp (mm) or mp, °C	Purified: bp (mm) or mp, °C; $n^{25}D$ or solvent[c]	Formula	Calcd (found): C, %	H, %	S, %
1	CH_2CO_2H	B C	46 94	125–142 (0.25)	141–142 (0.25); 1.5483[d]	$C_4H_6O_3S_2$	28.90 (29.04)	3.64 (3.78)	38.58 (38.37)
2	$(CH_2)_2CO_2H$	C	80	52–62	66–67; M	$C_5H_8O_3S_2$	33.32 (33.27)	4.47 (4.36)	35.58 (35.42)
3	$(CH_2)_3CO_2H$	C	93	130–140 (0.25)	1.5350[d]	$C_6H_{10}O_3S_2$	37.09 (37.34)	5.19 (5.30)	33.01 (32.71)
4	$(CH_2)_4CO_2H$	C	97	e	33–34[e]	$C_7H_{12}O_3S_2$	40.36 (40.30)	5.81 (5.79)	30.79 (30.60)
5	$(CH_2)_2N^+H_3Cl^-$	C	85	90–95	103–104; D	$C_4H_{10}ClNOS_2$[f]	25.59 (25.68)	5.37 (5.24)	34.16 (33.94)
6	$CH_2CH{=}CH_2$	C	77	45–53 (0.5)	45 (0.5); 1.5394	$C_5H_8OS_2$	40.51 (40.80)	5.44 (5.71)	43.26 (43.29)
7	o-HO_2CPh	C	93	120–170	178–180; Ch-C	$C_9H_8O_3S_2$	47.35 (47.28)	3.53 (3.47)	28.09 (27.95)
8	$(CH_2)_2CO_2Me$		65	1.5184[g]	1.5187[e]	$C_6H_{10}O_3S_2$	37.09 (37.30)	5.19 (5.25)	33.01 (32.79)
9	$(CH_2)_2N^+H_2$-n-$C_{10}H_{21}$ Cl^-	A	82	150–160 dec	180 dec; M-Et	$C_{14}H_{30}ClNOS_2$[f]	51.27 (51.54)	9.22 (9.33)	19.55 (19.32)
10			16	68–71	74–76;[h] E				
11	$CH_2CH_2CH_3$	B	94	50–54 (2.0)	54 (2.0); 1.5155	$C_5H_{10}OS_2$	39.96 (40.00)	6.71 (6.72)	42.68 (42.70)

[a] Method A where X = H, Y = SO_2R; B, where X = H, Y = Cl; and C where X = Cl, Y = H. [b] Sulfenyl chlorides were not isolated; yields reported are based on the assumption of 100% conversion to the sulfenyl chloride. [c] Solvents used for recrystallization: Ch, chloroform; C, carbon tetrachloride; M, methylene chloride; D, dioxane; Et, ethyl ether; E, absolute ethanol. [d] Purification was effected by column chromatography on silica gel using hexane–ethyl ether (2:3). [e] The crude product was a viscous oil that could neither be distilled nor crystallized. Pure product was obtained by column chromatography on silica gel using 1:1 carbon tetrachloride–chloroform. [f] Analyses for Cl and N, respectively, calcd (found) for **5** were 18.89 (19.06), 7.46 (7.54), and for **9** 10.81 (10.53), 4.27 (4.35). S. J. Brois, J. F. Pilot, and H. W. Barnum reported a similar synthesis of **5** after this paper had been submitted, mp 101–103° [*J. Amer. Chem. Soc.*, 92, 7629 (1970)]. [g] Crude $n^{25}D$. [h] Lit.[11a] 77°.

for the preparation of **2**, **7**, and **9** (eq 2).[4] All yields

$$Pb(SCN)_2 + Br_2 \longrightarrow (SCN)_2 \xrightarrow{AcSH} \underset{\mathbf{12}}{AcSSCN} \xrightarrow{RSH} AcSSR \quad (2)$$

were low (17, 14, and 11%, respectively), and difficulty was encountered in removing residual SCN-containing compounds. An attempt to isolate acetylsulfenyl thiocyanate (**12**) in the hope of obtaining a useful, relatively stable precursor was unpromising.

The procedure of Mukaiyama and Takahashi was unsatisfactory in our hands for the preparation of liquid acetyl disulfides (eq 3).[5] An attempt to prepare phenyl

$$AcSH + EtO_2CN{=}NCO_2Et \longrightarrow \underset{\mathbf{13}}{EtO_2CN(SAc)NHCO_2Et} \xrightarrow{RSH} AcSSR \quad (3)$$

acetyl disulfide by this procedure was unsuccessful, as was an attempt to purify the intermediate **13**; the nmr spectrum of the distilled **13** had appropriate peaks, but the ratios of protons were inconsistent with pure **13**. When the addition was reversed, benzenethiol being added first, 44% of phenyl acetyl disulfide was isolated (the ir spectrum was identical with that of an authentic[2g] sample). Tlc, however, indicated that all fractions contained both symmetrical disulfides and the unsymmetrical one. Because of the low yield and purification problems, further work with this method was not indicated.

Unsymmetrical disulfides have been prepared by exchange between a thiol and a symmetrical disulfide.[6] In trying this method, we sought, in the usual way, to drive the reaction toward completion by distilling the more volatile thiol (eq 4). This method was unsuccessful when attempted with benzenethiol (bp 169°) and acetyl disulfide [bp 40–47° (1.5 m)]. Both acetyl disulfide and phenyl acetyl disulfide should be susceptible to nucleophilic attack at either the –SS– bond or the –C(O)S– bond. Attack at the latter would lead to polysulfides, which would subsequently decompose. When the reaction mixture was heated above the boiling point of thioacetic acid (bp 93°), it darkened and no distillate was obtained.

$$PhSH + (AcS)_2 \longrightarrow AcSSPh + AcSH \quad (4)$$

Acetyl p-toluenethiolsulfonate (**14**) was a possible intermediate for the preparation of acetyl disulfides according to eq 5. It evidently resulted from the re-

$$RSH + \underset{\mathbf{14}}{p\text{-}CH_3C_6H_4SO_2SAc} \xrightarrow{Et_3N} AcSSR + p\text{-}CH_3C_6H_4SO_2^-Et_3NH^+ \quad (5)$$

action of both potassium p-toluenethiolsulfonate[7] with acetyl chloride and of anhydrous sodium p-toluenesulfinate with acetylsulfenyl chloride. Identical oils were obtained (ir spectra) in yields of ~70–88%. The oils, dried to remove acetyl-containing compounds, had ir spectra consistent with **14**, but tlc indicated two components. Attempts to crystallize **14** were unsuc-

(4) R. G. Hiskey, F. I. Carroll, R. M. Babb, J. O. Bledsoe, R. T. Puckett, and B. W. Roberts, *J. Org. Chem.*, **26**, 1152 (1961).

(5) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

(6) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, **73**, 3627 (1951).

(7) *Cf.* B. G. Boldyrev and T. A. Trofimova, *J. Gen. Chem. USSR*, **27**, 1088 (1957).

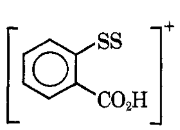
cessful, and chromatography led to decomposition. A precipitate soon formed that appeared to be bis(*p*-toluenesulfonyl) trisulfide. The EI mass spectrum of **14** showed no parent ion but did show peaks consistent with Ac, C_7H_7, $C_7H_7SO_2$, $AcSSO_2$, and SO_2H. The identity as **14** was confirmed by treating the oil with 2-methyl-2-propanethiol; distillation gave pure *tert*-butyl acetyl disulfide (**15**) in 24% yield (ir spectrum and glpc).[3] Although pure **14** could not be isolated, all indications (ir, nmr, mass spectrum, and preparation of **15**) point to its existence, although it probably is unstable. Further work on this method was not attempted.

The procedure of Böhme and Clement was found to be elegant and generally applicable and is considered the method of choice.[8] It was used to prepare disulfides **1–7** (eq 6). Acetylsulfenyl chloride (**16**), prepared

$$Ac_2S + Cl_2 \xrightarrow{-AcCl} \underset{\mathbf{16}}{AcSCl} \xrightarrow{RSH} AcSSR \qquad (6)$$

from acetyl sulfide and chlorine (eq 6),[8] reacted smoothly with the appropriate thiol to give **1–7** (*cf.* Table I); no base catalyst was needed. Care had to be taken to maintain the temperature below −10° during preparation of **16**, because the reaction is very exothermic; higher temperatures led to significantly lower yields of acetyl disulfides. Distillation of **16** was not done because it led to large losses through decomposition and to products little purer than others prepared merely by evaporating acetyl chloride. The yields of **1–7** were 77–97%.

Of the group **1–7**, only **5** and **7** warrant comment. In the preparation of **5**, 2-mercaptoethylamine hydrochloride was sparingly soluble in CH_2Cl_2, but **5** dissolved and was isolated by solvent evaporation; absolute EtOH as the solvent gave **5** in only 14% yield. A previous attempt to prepare **7** by the reaction of thioacetic acid and *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate,[9a] a general procedure for characterizing thiols,[9b] gave a product having an appropriate ir spectrum. However, pure **7** could not be obtained, and there was considerable question as to the identity of the product.[9a] Comparison of ir spectra of this earlier product with that of **7** prepared by eq 6 showed both to be identical except for minor intensity differences. The mass spectrum of **7** conforms to a pattern outlined for unsubstituted carbonyl disulfides, with addition of certain peaks.[10] Ions consistent with the following assignments were found (intensity, %): M^+ (0.1%), Ac^+ (100%), **17** (0.7%), **18** (70%), **19** (43%), and AcSH (11%); isotopic cluster peaks were consistent with these assignments.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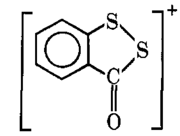
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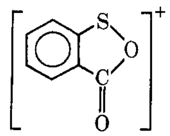
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(8) H. Böhme and M. Clement, *Justus Liebigs Ann. Chem.*, **576**, 61 (1952).

(9) (a) P. M. Giles, Jr., Ph.D. Dissertation, Vanderbilt University, May 1970, pp 31, 44; (b) L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971).

(10) W. S. Hanley, Ph.D. Dissertation, Vanderbilt University, Jan 1971, pp 30–32, 52–54.

Unpromising results ensued in only two preparations attempted by the Böhme–Clement method. Distillation of the product from **16** and 2-mercaptoethanol gave no β-hydroxyethyl acetyl disulfide (**20**). The product evolved hydrogen sulfide even at 0°. The hydroxyl group of **20** probably attacks the carbonyl group to give $AcO(CH_2)_2SSH$, which decomposes.[3] Acetonyl acetyl disulfide (**21**) evidently was obtained from **16** and α-mercaptoacetone (**22**, actually polymeric) in ~70% crude yield (ir spectra), but distillation or chromatography afforded no pure **21**; possibly **16** reacted with α hydrogen atoms of the ketone to give impurities.

In the other preparations, the ester **8** was prepared from **2** with diazomethane, evidently with side reactions since the yield was only 65%. The *n*-decylaminoethyl compound **9** was prepared by thioalkylation of thioacetic acid with the appropriate thiolsulfonate; an attempt to purify **9** after treatment of **16** with 2-(*n*-decylamino)ethanethiol was unpromising. The 1,2-dithiole-3-one **10** has been prepared by several methods.[11] We obtained **10** from **7** using HCl in ethanol in a method resembling one of Raoul and Vialle;[11c] the yield was lower (16%) than that of **10** prepared by their method (95%) based on the ester rather than the acid.

Purification of **1–11** presented no great problems. Solids could be recrystallized (**2**, **5**, **7**, **9**, **10**), and two liquids (**6**, **11**) could be distilled using a highly efficient column. Compounds **1** and **3** were oils which could be distilled through a short Vigreux column but with slight decomposition; hence they were chromatographed, as were **4** and **8**.

The purity of disulfides **1–11** was assured by observation of single spots after tlc. (In five instances, when the two symmetrical disulfides were added to the unsymmetrical one, all three spots could be resolved.) With **6**, **8**, and **11** as examples, only single peaks also were observed after glpc. Accordingly, products contained no symmetrical disulfides from disproportionation (eq 7).

$$2AcSSR \rightleftharpoons (AcS)_2 + (RS)_2 \qquad (7)$$

The structures of the disulfides were confirmed in several ways: by ir spectra (loss of absorption of –SH at ~2550 cm^{-1}, retention of absorptions associated with the remainder of the thiol, and presence of absorptions associated with the carbonyl moiety at ~1730, 1110, and 940 cm^{-1});[10] by nmr spectra (loss of the peaks at δ ~1.4 for –SH, with retention of the correct number and relationship of protons); by elemental analysis; and, for **7**, by mass spectrometry.[10]

The decomposition of compounds **2**, **5**, **6**, **8**, **9**, **11**, 2-acetamidoethyl acetyl disulfide (**23**), and β-chloroethyl acetyl disulfide (**24**)[3] was studied in dioxane (100°). Water or ethanol could not be used because of hydrolysis and ethanolysis of the acetyl disulfides at 100°.[3] Propyl acetyl disulfide (**11**) was used as a reference for the other β-substituted ethyl acetyl disulfides, since the β-methyl group affords a good base point for comparison with other β substituents. That a 2-acetamidoethyl disulfide decomposes more rapidly than an analogous alkyl disulfide, we think because of a neighboring-group participation of AcNH–,[3] was con-

(11) (a) A. Schonberg and A. Mostafa, *J. Chem. Soc.*, 793 (1941); (b) E. W. McClelland, L. A. Warren, and J. H. Jackson, *ibid.*, 1582 (1929); (c) P. Raoul and J. Vialle, *Bull. Soc. Chim. Fr.*, 1670 (1959).

TABLE II
THERMAL REACTIVITIES OF SUBSTITUTED ACETYL DISULFIDES, $AcSS(CH_2)_2X$[a]

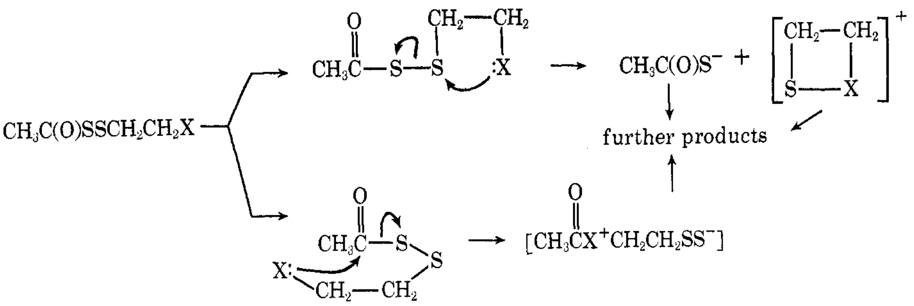
Compd	X	Time, days	Decomposition, %,[b] based on $AcSS(CH_2)_2X$	$(SCH_2CH_2X)_2$
5	$NH_3^+Cl^-$	2	100	100[c]
9	NH_2^+-n-$C_{10}H_{21}Cl^-$	1		>58[c,d]
		2		>56[c,d]
23	NHAc	2	30[c,e]	
2	CO_2H	2	0[c]	
		8	20[c]	
8	CO_2Me	3	12[f]	
		7[g]	28[f]	
		14[g]	37[f]	
24	Cl	7	14[f]	
		14	14[f,h]	
6	$=CH_2$	14	15[f]	
11	CH_3	14	19[f]	

[a] Determined in anhydrous dioxane at 100° in the dark. [b] $AcSS(CH_2)_2X$ is starting material recovered by isolation or glpc. The value for $(SCH_2CH_2X)_2$ is based on separated material (*cf.* Experimental Section). Values calculated either as 100% − % $AcSS(CH_2)_2X$ recovered *or* by using the following equation based on eq 7: per cent decomposition = 2·[mmol of $(-SCH_2CH_2X)_2$](100)/(mmol of $AcSSCH_2CH_2X$). [c] Determined by isolation. [d] Compound 9 could not be isolated from the reaction solution. It is likely that 9 also decomposed by a secondary pathway to give products other than 2-(n-decylamino)-ethyl disulfide dihydrochloride. The per cent decomposition therefore is shown as >58%. [e] Compound 23 was prepared previously;[2g] 23 prepared according to eq 6 was identical with this previous 23. [f] Determined by glpc. [g] Values for 21 and 25 days were 28 and 36%, respectively. [h] Average of 12 and 17 days (11 and 16%, respectively).

firmed by comparing 2-acetamidoethyl with propyl acetyl disulfide (**23** and **11**). Earlier studies on **23**, by analyzing for 2-acetamidoethyl disulfide, showed decomposition as follows (days, %): 1, 22; 2, 32.[2g] We confirmed this result by isolating **23** (2, 30). Decomposition of the propyl analog **11** was far slower: 9, 8; 14, 19; 18, 21; and 35, 26.

would vary predictably in their resistance to decomposition, thereby further supporting a functional-group assistance by carboxylate. Such a difference was seen in the more rapid disproportionation of the salt of *o*-(phenyldithio)benzoic acid than of the acid itself or of the salt of its meta isomer.[1a] Unfortunately, the acetyl moiety was so labile that we could not prepare carboxylate salts. Thus, after **2** had been neutralized with sodium ethoxide in ethanol, immediate addition of ether gave a precipitate which had completely lost the carbonyl absorption (1730 cm^{-1}) and the other usual absorptions of **2** (1100, 940 cm^{-1}); evidently **2** decomposed within 5 min. Acidification of the precipitated salt gave 3,3-dithiodipropionic acid (~100% yield). In order to learn whether the ethoxide ion had led first to the carboxylate salt or whether it had first attacked the acetyl group directly, a mixture of the propyl analog **11** and 1 equiv of acetic acid was treated with 1 equiv of sodium ethoxide. After about 15 min, tlc showed that no **11** remained. Triethylamine and *n*-butyllithium, employed similarly with **11** and acetic acid in dioxane, caused **11** to decompose appreciably within 24 hr and 5 min, respectively. They therefore seemed unsuitable also for formation of carboxylate salts. Lithium acetate and lithium hydride were too sparingly soluble in dioxane to be useful.

The increased reactivity (days, per cent decomposition) of the amine salts **5** (2, 100) and **9** (2, >58) over that of the amide **23** (2, 30) is consistent with orders of reactivity for related disulfides.[2] This relationship most likely results from free amine in equilibrium with **5** and **9**, which is more nucleophilic than the amide. The stability of the acid **2** (8, 20) presumably stems from low nucleophilicity of a carboxyl group largely undissociated in dioxane; the stability of the ester **8** is similar (7, 28). The reactivities of **24** (14, 14), **6** (14, 15), and **11** (14, 19) are similar, indicating very little assistance by Cl and $=CH_2$.



(8)

Results of the decompositions are shown in Table II. It should be emphasized that most products probably were not merely the symmetrical disulfides predicted by eq 7, but a mixture that reflects reactions concurrent with disproportionation, since both the –SS– bond and –C(O)S– bond are susceptible to attack by nucleophiles (eq 8; *cf.* ref 3 for discussion of the complex decomposition of acyl disulfides). The order of increasing resistance to decomposition (and hence of decreasing effect of the functional group) was: $NH_3^+ \sim NH_2^+$-*n*-decyl < HNAc < $CO_2H \sim CO_2Me$ < Cl ~ $=CH_2 \sim CH_3$.

We had hoped that the salts of the carboxylic acids **1–4** would both react more rapidly than the acids and

In vitro tests on **1–11** and **23** against *Histoplasma capsulatum*, a fungal pathogen for man, were not very promising.[12] The best inhibitors in μg/ml were: **6**, 5–10; **9**, 10; **10**, 10; **11**, 10–20; **5**, 15; **8**, 15; **1** and **23**, 20. Compounds **2–4** and **7** were inactive at 20 μg/ml. Evaluations of *in vivo* activities of **1–4** showed weak but statistically significant activity (up to 12–14% extension of survival, *vs.* 31% for amphotericin B at a lower dose level).[13a]

(12) Tested as described previously;[3] we are indebted to S. Evans for these tests.
(13) (a) Tests kindly arranged by Dr. W. B. Lacefield and carried out under the supervision of Dr. R. S. Gordee of Eli Lilly and Co., as described earlier;[3,13b] (b) *cf.* R. S. Gordee and T. R. Matthews, *Bacteriol. Proc.*, 114 (1969).

Experimental Section[14]

Materials.—Purified o-mercaptobenzoic acid (Aldrich Chemical Co.) was kindly provided by Dr. P. M. Giles, Jr.,[9] and 5-mercaptovaleric acid by Dr. Y. H. Khim. 2-(n-Decylamino)ethyl 2-(n-decylamino)ethanethiolsulfonate dihydrochloride (**25**) was kindly provided by the Walter Reed Army Institute of Research. The following were prepared by published procedures: acetyl sulfide [86% yield, bp 56° (17 mm), n^{25}D 1.4748; lit.[15] bp 62–63° (20 mm), n^{21}D 1.4810]; 2-acetamidoethanethiol [74% yield, bp 86° (1.5 mm); lit.[16] bp 138–140° (7 mm)]; and 4-mercaptobutyric acid [93% yield, bp 94° (0.5 mm); lit.[17] bp 105° (5 mm)]. All other materials were used as purchased.

α-Mercaptoacetone (22).—Compound **22** was prepared from α-chloroacetone and KSH in H_2O.[18] A product precipitated and was washed with H_2O, EtOH, and Et_2O to give a solid, mp 71–73° (lit.[18] mp 105–110°). Crude **22** had no carbonyl absorption (~1700 cm^{-1}) but did absorb at 3380 cm^{-1} (OH). Titration with 0.1 N aqueous KI_3 indicated 100% SH. The mass spectrum showed M^+ at m/e 90 (35%), $(M + 2)^+$ at m/e 92 (2%), and intense ions at m/e 43 (CH_3CO, 100%) and 47 (CH_2SH, 18%). An ion at m/e 180, $2M^+$ (0.1%), may indicate the presence of a dimer of **22**. The ir, high melting point, and very sparing solubility of **22** indicate a polymeric structure, such as a hemimercaptole, which in solution is in facile equilibrium with **22**. Virtual insolubility in EtOH and Et_2O suggests a larger structure than the dimer indicated by the mass spectrum.

Synthesis of Acetyl Disulfides (1–7, 9, and 11).—Except for variations noted in Table I, procedures A, B, and C were as illustrated.

Procedure A. 2-(n-Decylamino)ethyl Acetyl Disulfide Hydrochloride (9).—Thioacetic acid (11.1 g, 90% SH, 0.13 mol) was added (~10 min) to a suspension of **25** (70 g, 0.13 mol) in 1.0 l. of CH_2Cl_2, and the mixture was stirred for 24 hr. Solid was removed, and solvent was evaporated to leave 35 g (82%) of **9** as a white, waxy solid, mp 150–160° dec. Six recrystallizations from CH_2Cl_2–Et_2O gave **9** with a constant mp of 180° dec; tlc showed only one spot (R_f 0.73); ir (Nujol) 2940, 2770, 2450, 1740, 1595, 1470, 1380, 1115, 1060, 945, and 725 cm^{-1}.

Procedure B. 2-(Acetyldithio)acetic Acid (1).—Compounds **1** and **11** were prepared as described previously for alkanethiols.[3] For **1**, Cl_2 (3.1 g, 44 mmol) was added to thioglycolic acid (4.0 g, 44 mmol) in 50 ml of CH_2Cl_2 at −20°. Some precipitate formed but most had redissolved by the end of addition. This solution was added to thioacetic acid (3.8 g, 95% SH, 48 mmol) in CH_2Cl_2 at −20°, and the reaction mixture was allowed to warm to room temperature for 1.5 hr. The solvent was evaporated to leave 7.7 g (106% yield) of **1**, n^{25}D 1.5550. Pure **1** was afforded by column chromatography using silica gel (hexane–Et_2O): n^{25}D 1.5483; ir (neat) 2300–3700, 1720, 1690, 1410, 1350, 1280, 1190, 1105, and 935 cm^{-1}; nmr ($CDCl_3$) δ 2.5 (s), 3.6 (s), and 10.7 (s).

Procedure C. 3-(Acetyldithio)propionic Acid (2).—Essentially the method of Böhme and Clement was used to prepare **1–7**,[8] except that the sulfenyl chloride **16** was prepared in CH_2Cl_2 and used without isolation. Acetylsulfenyl chloride (**16**) was prepared under a N_2 atmosphere at −15° from Ac_2S (37 g, 0.31 mol) in 50 ml of CH_2Cl_2 and Cl_2 (21 g, 0.29 mol) in 75 ml of CH_2Cl_2. AcCl formed in the reaction was evaporated under reduced pressure (~20 mm, 15 min), and the residual solution (~0.5 of the original volume) of **16** was added to 3-mercaptopropionic acid (30 g, 0.28 mol) in ~125 ml of CH_2Cl_2 at −10°. The reaction mixture was stirred for 1 hr at room temperature, and then the solvent was evaporated to give 40 g (80%) of crude **2**, mp 52–62°. Four recrystallizations from CH_2Cl_2 afforded **2** with constant mp 66–67°; ir (Nujol) 2300–3300, 1730, 1700, 1460, 1410, 1380, 1350, 1330, 1285, 1260, 1195, 1100, 940, 905, 760, and 645 cm^{-1}; nmr ($CDCl_3$) δ 2.5 (s), 2.6–3.1 (m), and 10.4 (s).[19]

Methyl 3-(Acetyldithio)propionate (8).—Diazomethane[20] (~80 mmol) was added to a stirred solution of **2** (8 g, 44 mmol) in 100 ml of absolute Et_2O. The solution was stirred for 5 min and AcOH was added to destroy the excess CH_2N_2. The solution then was washed with H_2O, 5% $NaHCO_3$, and again with H_2O to neutrality, and was dried ($CaSO_4$). Evaporation left 5.6 g (65%) of **8** as a reddish liquid. Column chromatography on silica gel using CCl_4–$CHCl_3$ gave pure **8** in 50% yield, n^{25}D 1.5187; tlc showed only one spot (R_f 0.53), and a single peak was observed by glpc (R_t ~194 sec, oven temperature 112°); ir (neat) 2965, 1735, 1700, 1440, 1360, 1250, 1115, and 940 cm^{-1}; nmr (CCl_4) δ 2.4 (s), 2.5–3.1 (m), and 3.6 (s).

Acetylsulfenyl Thiocyanate (12).—Thioacetic acid (8.0 g, 95% SH, 0.1 mol) was added at 0° to $(SCN)_2$ (12 g, 0.1 mol), prepared from $Pb(SCN)_2$ and Br_2 in 1.0 l. of Et_2O.[4] The solution was stirred for 15 min and then was washed rapidly with cold H_2O, 5% $NaHCO_3$, and again with H_2O to neutrality, and was dried ($CaSO_4$). Evaporation left 12 g (90%) of a reddish liquid, bp 44° (0.75 mm). The ir and nmr spectra were consistent with **12**: ir (neat) 2980, 2920, 2020, 1735, 1420, 1350, 1100, and 940 cm^{-1}; nmr (CCl_4) δ 2.48 (s) (nmr also showed slight impurities); tlc (benzene) indicated one large (R_f ~0.6) and one very small spot. Elemental analysis was far from the theoretical value despite shipping in Dry Ice. *Anal.* Calcd for $C_3H_3ONS_2$: C, 27.05; H, 2.27. Found: C, 30.91; H, 4.46. Samples of the distilled **12** formed a precipitate during 36 hr at ambient conditions, but at 0° remained homogeneous for about 1 week and showed no change in ir. No attempt was made to identify decomposition products since the **12** seemed too unstable for practical use.

Decomposition of Acetyl Disulfides.—The resistance of disulfides **2, 5, 6, 8, 9, 11, 23**, and **24** to decomposition was determined by the general procedures below, the per cent decomposition being determined by glpc analysis for **6, 8, 11**, and **24**, and by isolation for **2, 5, 9**, and **23**. In all experiments, concentrations were 1.0 mmol of disulfide in 10 ml of dioxane.

A. By Glpc.—Glpc was performed as usual (oven temperatures for **6** and **11**, 82°; for **8** and **24**, 112°).[3] Typical retention times (sec) for various components at 82 or 112° (*) were: dioxane, 19, 12*; 1,2,4-trichlorobenzene (internal standard) ~200, 69*; **6**, 120; **8**, 194*; **11**, 137; and **24**, 89*.

Illustratively, disulfide **6** (0.1541 g, 1.0 mmol) and 1,2,4-trichlorobenzene (0.1815 g) were dissolved in 10 ml of dioxane, and 1-ml aliquots were sealed in each of ten ampoules. The ampoules were wrapped in aluminum foil for protection against light and were heated at 100°. After a time t, 1.0 μl from an ampoule was injected on the glpc column. The per cent recovery was calculated from the automatic peak-area output of the instrument by using the expression $[(6 \text{ at time } t)(100)/(Cl_3C_6H_3 \text{ at time } t)]/[(6 \text{ at } t_0)/(Cl_3C_6H_3 \text{ at } t_0)]$.

The data given below are in order of per cent recovery and of time t in days at 100° (in parentheses): **6**, 96 (5), 95 (9), 85 (14), 86 (18), and 72 (26); **8**, 88 (3), 72 (7), 63 (14), 83 (19), 72 (21), and 64 (25); **11**, 100 (5), 92 (9), 81 (14), 79 (18), and 74 (35); and **24**, 86 (7), 85 (11), 89 (12), and 84 (17). The per cent decomposition (Table II) was calculated by subtracting the per cent recovery from 100.

B. By Isolation.—The disulfide (1.00 mmol) was dissolved in 10 ml of dioxane in a glass ampoule, which was sealed, wrapped, and heated as before for the periods stated in Table II. The contents then were removed from the ampoules and freeze-dried to constant weight at ~0.01 mm (24 hr). Decomposition products were separated as described below for the various disulfides and were dried to constant weight. The results are given in Table II. Materials for which values are given were identified by ir spectra, melting points, and mixture melting points (*vs.* authentic disulfide). With **2**, the dried product was washed with 5 ml of CH_2Cl_2 to separate **2** from nearly insoluble 3,3′-dithiodipropanoic acid. With **5**, cystamine dihydrochloride, which precipitated from solution, was separated by filtration. With **9**, the dried product was washed with CH_2Cl_2 to remove **9** from the insoluble 2-(n-decylamino)ethyl disulfide dihydrochloride. With **23**, the dried product was washed with 5 ml of Et_2O to separate **23** from the insoluble N,N′-diacetylcystamine.[2g]

Registry No.—**1**, 30768-33-3; **2**, 29070-80-2; **3**, 30768-35-5; **4**, 30826-40-5; **5**, 30453-32-8; **6** 30768-37-7; **7**, 30768-38-8; **8**, 30826-41-6; **9**, 30768-39-9; **10**, 1677-27-6; **11**, 5824-50-0; **12**, 30768-42-4; **22**, 24653-75-6.

(14) Experimental details were as given in a previous paper,[3] except that melting points were taken using a Mel-Temp hot-block apparatus and that typical solvents used for tlc were benzene, MeOH, and $CHCl_3$.

(15) W. A. Bonner, *J. Amer. Chem. Soc.*, **72**, 4270 (1950).

(16) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

(17) Kodak Soc., Belgian Patent 593,048 (1960); *Chem. Abstr.*, **55**, 14142 (1961).

(18) M. Ohta, *J. Pharm. Soc. Jap.*, **70**, 709 (1950); *Chem. Abstr.*, **45**, 6581 (1951).

(19) After completion of this paper, we learned of a synthesis of **2** by a similar method but with a large excess of distilled **16** [J. Tsurugi, Y. Abe, and S. Kawamura, *Bull. Chem. Soc., Jap.*, **43**, 1890 (1970)]: 69–70°; ir (KBr) 1690 cm^{-1}; nmr ($CDCl_3$) δ 2.49 ($SCOCH_3$), 11.70 (COOH).

(20) T. J. DeBoer and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **73**, 229 (1954).