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Reactions of Ketene Thioacetals with Electrophiles. A Method for Homologation of Aldehydes

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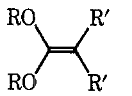
The reactions of ketene thioacetals of general structures **6** and **9** with a number of electrophilic reagents are described. The reagents examined included thiocyanogen, positive bromine and chlorine sources, 2,4-dinitrobenzenesulfenyl chloride, *p*-nitrobenzenediazonium fluoroborate, diethyl azodicarboxylate, and chlorosulfonyl isocyanate. All reactions proceeded with substitution of the electrophile for the vinyl proton with retention of the ketene thioacetal skeleton. Ketene thioacetals **9a–c** were converted to thioacetals of aldehydes by a protonation–hydride transfer process using organosilicon hydrides in acidic media as a key step in an aldehyde homologation sequence. The reactions of ketene thioacetals under these conditions involve cationic intermediates stabilized by electron donation from sulfur.

The chemical reactivity of alkenes bearing multiple electron-releasing heteroatom substituents on the double bond has been an area of continuous investigation for many years.[2] The many possible combinations of alkyl, alkylamino, alkyoxy, and alkylthio substituents give rise to a group of compounds possessing variable chemical reactivity with respect to properties such as ability to function as a nucleophile toward alkyl and acyl halides, electron-donating ability, and stability of charge-transfer complexes. Generally, the timing of the studies has paralleled the availability of efficient synthetic routes to compounds of the desired substitution pattern with the most notable investigations to date being centered on ketene acetals (**1**)[3] and tetraaminoethylenes (**2**).[4]



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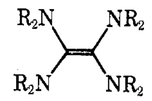

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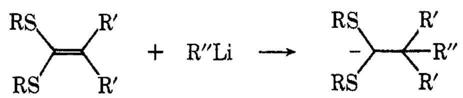
Our interest has been directed toward ketene thioacetals (**3**), since several routes to these compounds have been developed recently[5] and such compounds could be useful as synthetic intermediates, particularly if methods for subsequent modification were available. Such a potentially useful transformation has been reported by Carlson[6] and involves nucleophilic addition of organolithium reagents to **3**.



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The resulting carbanion may then be used for further transformations. This reaction takes advantage of the known ability of sulfur to stabilize adjacent carbanions,[5a,7] while the reactions to be described here for modification of ketene thioacetals utilize the ability of sulfur to stabilize adjacent carbonium ions.[8,9]

Results and Discussion

Synthesis of Ketene Thioacetals.—On reaction with trimethyl phosphite the cyclic trithiocarbonates **4** and **7** undergo desulfurization at thione sulfur to afford ylides **5** and **8**, which have been shown to react with aldehydes in the Wittig fashion yielding ketene thioacetals of types **6** and **9**.[5b]

Compounds **6**, **9a**, and **9b** have been reported previously,[5b] while **9c** was prepared in 63% yield by the

(1) (a) Author to whom inquiries should be addressed; (b) NDEA Title IV Fellow, 1966–1969.

(2) For a review on electron-rich olefins, see R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **7**, 754 (1968).

(3) S. M. McElvain and P. L. Weyna, *J. Amer. Chem. Soc.*, **81**, 2579 (1959), represents the 37th paper from McElvain's group spanning a period of 23 years.

(4) Reviews: N. Wiberg, *Angew. Chem., Int. Ed. Engl.*, **7**, 766 (1968); D. M. Lemal in "Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 12, p 701.

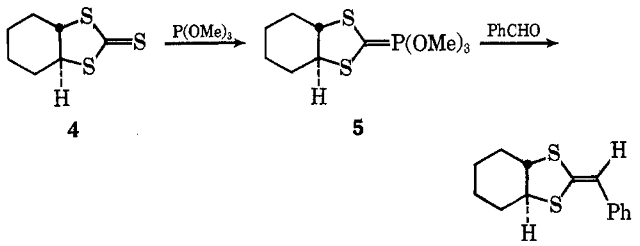
(5) (a) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); (b) E. J. Corey and G. Märkl, *Tetrahedron Lett.*, 3201 (1967); K. I. Jensen and L. Henriksen, *Acta Chem. Scand.*, **22**, 1107 (1968).

(6) R. M. Carlson and P. M. Helquist, *Tetrahedron Lett.*, 173 (1969).

(7) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 71–84.

(8) W. L. Tucker and G. L. Roof, *Tetrahedron Lett.*, 2747 (1967); R. A. Olofson, S. W. Walinsky, J. P. Marino, and J. L. Jernow, *J. Amer. Chem. Soc.*, **90**, 6554 (1968); D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969); C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1964, Chapters 1 and 2.

(9) For a dissenting view regarding the importance of such stabilization see R. L. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, **90**, 4924 (1968).



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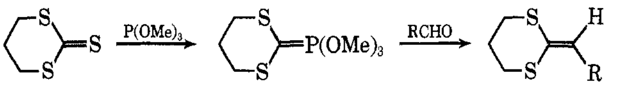


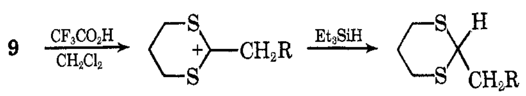
7 8 9a, R = *n*-Pr
b, R = *p*-NO_2Ph
c, R = ferrocenyl

same procedure. Attempts to bring about reaction of **8** with indole-3-carboxaldehyde were unsuccessful.

Ketene thioacetals bearing electron-withdrawing substituents (**10** and **11**)[10] may be prepared readily by other methods but are unreactive toward electrophiles and will not be discussed further.

10 11

Aldehyde Homologation.—A useful modification of a ketene thioacetal would be reduction of the double bond, since this would afford, in the case of **9**, the cyclic trimethylene thioacetal of an aldehyde having one more carbon atom than the aldehyde used for condensation with the ylide. Since a number of methods are available for conversion of such acetals to the aldehyde,[11] the overall process would constitute an aldehyde homologation sequence. Based on previous experience with organosilicon hydrides as hydride donors,[12] we chose to effect hydrogenation of the double bond by the protonation–hydride transfer route shown in eq 1.

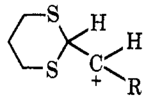


(1)

12 13a, 48%
b, 85%
c, 64%

Ketene thioacetals **9a–c** were all found to be readily protonated by trifluoroacetic acid in methylene chloride solution to give stable carbonium ions. In the presence of triethyl- or triphenylsilane, carbonium ions **12a–c** were converted to **13a–c** in moderate to good yields within 24 hr at 25°. Compounds **13a–c** were characterized by elemental analysis and nmr, ir, and mass spectra (see Experimental Section) and in the case of **13a** the structure was confirmed by independent synthesis from valeraldehyde and 1,3-propanedithiol.

While the mechanism of the protonation–hydride transfer sequence was not explicitly studied, it seems likely on the basis of the reactions with acid and electrophiles to be discussed shortly that it does occur *via* ion **12** rather than the alternative ion **14**.



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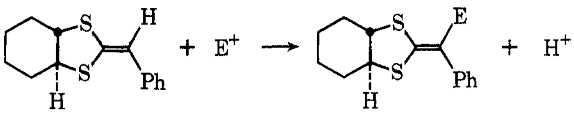
Thus, addition of trifluoroacetic acid to a solution of **6**, **9a**, or **9c** in deuteriochloroform in an nmr tube resulted in the disappearance of the vinyl proton signal. With **9c**, where ion **14** (R = ferrocenyl) should be particularly stable, the nmr spectrum is more consistent with **12** as the correct structure, since the signals resulting from the methylene protons α to the two sulfur atoms in the ring are shifted downfield by 0.6 ppm on addition of trifluoroacetic acid while the sharp singlet arising from five of the cyclopentadienyl ring protons is unchanged in position, and the signals from two pairs of nonequivalent cyclopentadienyl protons are shifted *upfield* 0.4 and 0.1 ppm.

It was also possible to bring about hydrogen–deuterium exchange of the vinyl proton of **6** by addition of trifluoroacetic acid-*d* to a solution of **6** at 25°. This exchange constitutes good evidence for the intermediacy of carbonium ions stabilized by the two sulfur atoms.

Attack by Electrophilic Reagents.—Reaction of **6** with a variety of electrophiles proceeds rapidly and cleanly according to the general equation



(2)

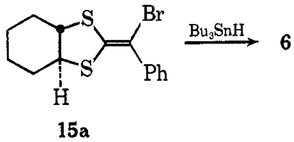
6 15

These reactions are summarized in Table I and details are given in the Experimental Section.

TABLE I
REACTIONS OF KETENE THIOACETAL 6 WITH ELECTROPHILES

Reagent	E in eq 2	Yield, %
Bromine in carbon tetrachloride	Br, **15a**	81
N-Bromosuccinimide	Br	78
Pyridinium bromide perbromide	Br	67
N-Chlorosuccinimide	Cl, **15b**	51
Thiocyanogen	-SCN, **15c**	82
2,4-Dinitrobenzenesulfenyl chloride	2,4-$(NO_2)_2$PhS-, **15d**	70
Diethyl azodicarboxylate	-N($NHCO_2Et$)—CO_2Et, **15e**	79
p-Nitrobenzenediazonium fluoroborate	*p*-NO_2PhN=N-, **15f**	58
Chlorosulfonyl isocyanate	-C(=O)—$NHSO_2Cl$	

In addition to the usual spectral and elemental composition data the structure of the bromination product was established by reconversion to **6** in 56% yield using tri-*n*-butyltin hydride, thereby demonstrating the re-

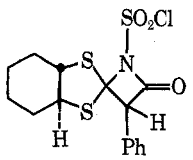


15a

(10) R. Gompper and W. Elsner, *Justus Liebigs Ann. Chem.*, **725**, 73 (1969).
(11) B. W. Erickson, Ph.D. Thesis, Harvard University, 1970, reviews existing methods for hydrolysis of thioacetals and describes several new techniques. See also D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966); E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).
(12) F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **36**, 758 (1971), and references cited therein.

tention of the ketene thioacetal structure and absence of skeletal rearrangement.

Bromination of **6** was effected with a number of reagents, including molecular bromine, *N*-bromosuccinimide, and pyridinium bromide perbromide. Similarly, *N*-chlorosuccinimide yielded **15b** and the pseudohalogen thiocyanogen yielded **15c**. The bright red azo compound **15f** resulted from reaction with *p*-nitrobenzenediazonium fluoroborate. Attempts were made to prepare cyclic adducts such as **16** with chlorosulfonyl isocyanate without success. While ready reaction oc-



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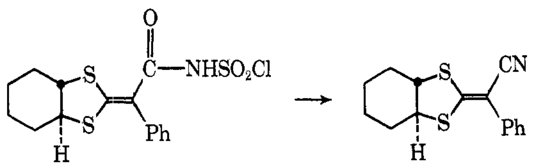
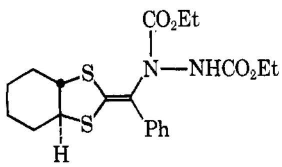
curred, the only isolable product appeared to be **15g** which was difficult to purify and decomposed to cyanoketene thioacetal **17**.



15g **17**

Diethyl azodicarboxylate also reacted readily with **6** but again no cyclic adduct was obtained, the product being **15e** as evidenced by its ir spectrum, which showed N–H stretching at 3.0 μ.

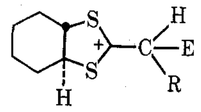


15e

Tetracyanoethylene also failed to yield a cyclic adduct with **6**. On mixing **6** and TCNE in either methylene chloride or benzene a dark green color formed immediately but no adduct was obtained. Examination of a solution of **6** and TCNE in deuteriochloroform by nmr showed that no gross reaction had occurred.[13]

A few reactions of ketene thioacetals of type **9** with electrophiles were carried out to determine whether the reactions undergone by **6** were typical of this general class of compounds or resulted from features, such as stereochemistry, which were unique to **6**. 2-Butylidene-1,3-dithiane (**9a**) reacted very similarly to **6** with 2,4-dinitrobenzenesulfenyl chloride and formed a dark purple azo compound with *p*-nitrobenzenediazonium fluoroborate.

The ease with which these electrophilic substitution reactions take place almost certainly results from stabilization of intermediates **18** and **19** by electron release from sulfur. The means by which this electron release is effected is, however, not clear. As Autrey and



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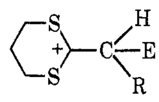
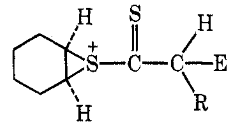


19

Scullard[9] have pointed out, there is little theoretical justification for the notion that electron donation from sulfur will be significant, since this would require a relatively unfavorable overlap of sulfur 3p orbitals with carbon 2p orbitals. We feel that the required 3p–2p orbital overlap could be important in these intermediates if the presence of the positive charge brought about a shortening of the carbon–sulfur bond to a more favorable length for overlap. Another explanation which we have considered is the possibility of stabilization resulting from formation of intermediate **20** from **18** and **21** from **19**.



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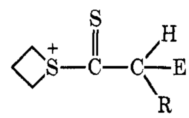

21

Ion **18** is oriented in the correct geometry for formation of **20** in that it has a trans arrangement of the two sulfurs, while formation of **21** from **19** would require a front-side displacement at carbon. Since both ketene thioacetal systems afford similar products on reaction with electrophiles, this explanation appears unlikely.

It was found in the course of this study that ketene thioacetals react only with relatively good electrophiles. Attempts at carbon–carbon bond formation by alkylation with benzyl chloride were unsuccessful.

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr disks for solids and pressed films for liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV.

Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

Ketene thioacetals **6**, **9a**, and **9b** were prepared as described by Corey and Märkl.[5b]

2-Ferrocenylidene-1,3-dithiane (**9c**).—Trimethyl phosphite (25 ml) was distilled into a flask containing 5.0 g (33.3 mmol) of trimethylene trithiocarbonate and the solution was stirred under N_2 at 55° for 3 hr. Ferrocenecarboxaldehyde (7.13 g, 33.3 mmol) was added and the reaction mixture was stirred at 55° overnight. The excess phosphorus esters were removed by hydrolysis with sodium hydroxide in 400 ml of 1:1 methanol–water on the steam bath and the resulting solution was poured into ice and extracted (CH_2Cl_2), dried ($NaSO_4$), filtered, and evaporated. The residue was chromatographed on alumina and eluted with chloroform to yield 6.54 g (63%) of **9c**: mp 82–84°; nmr ($CDCl_3$) δ 6.59 (s, 1, vinyl), 4.60 (t, 2, cyclopentadienyl), 4.20 (t, 2, cyclopentadienyl), 4.12 (s, 5, cyclopentadienyl), 2.91 (t, 4, J = 6 Hz, $-SCH_2$), and 2.4–1.9 (m, 2, $-CH_2-$).

An analytical sample, mp 88.5–90°, was obtained by recrystallization from ethanol–methylene chloride.

Anal. Calcd for $C_{15}H_{16}FeS_2$: C, 56.97; H, 5.10; S, 20.28; Fe, 17.66. Found: C, 56.82; H, 5.27; S, 20.50; Fe, 17.52.

Reduction of Ketene Thioacetals 9a–c by Hydride Transfer. 2-Butylidene-1,3-dithiane (**9a**).—Trifluoroacetic acid (2.14 ml, 28.8 mmol) was added to a stirred solution of **9a** (1.00 g, 5.75 mmol) in 10 ml of methylene chloride followed by 1.65 g (6.3

(13) Similar behavior of a ketene thioacetal with TCNE has been reported previously and interpreted as arising from formation of a charge-transfer complex: D. L. Coffen and P. E. Garrett, *Tetrahedron Lett.*, 2043 (1969).

mmol) of triphenylsilane. After 10 hr solid sodium bicarbonate was added, the solution filtered through Celite, and the methylene chloride evaporated. The product 2-*n*-butyl-1,3-dithiane (**13a**) was obtained in 47% yield (470 mg) by distillation from the solid residue (Ph_3SiOH) through a short path apparatus, bp 73–80° (0.35 Torr). The product was identical (nmr, ir) with authentic material.

Authentic **13a** was prepared by adding 20 ml of boron trifluoride etherate slowly to 1.0 ml (1.08 g, 10 mmol) of 1,3-propanedithiol and 1.15 ml of valeraldehyde in an erlenmeyer flask. The solution was heated at 50° for 1 hr and then poured into *ca.* 300 ml of 10% sodium hydroxide solution and extracted with ether. After drying (Na_2SO_4) and evaporation the product was distilled to afford 468 mg (27%) of **13a**: bp 71–72° (0.4 Torr); nmr ($CDCl_3$) δ 4.1 (t, 1, $HC(S-)_2CH_2$), 2.8–3 (m, 4, $-SCH_2-$), 1–2.2 (broad m, methylenes), 0.9 (t, 3, $-CH_3$).

Anal. Calcd for $C_8H_{16}S_2$: C, 54.49; H, 9.15; S, 36.36. Found: 54.30; H, 9.07; S, 36.23.

2-(*p*-Nitrobenzylidene)-1,3-dithiane (9b).—To a methylene chloride solution (10 ml) containing 2.00 g (7.90 mmol) of **9b** and 1.01 g (8.6 mmol) of triethylsilane was added 1.17 ml (15.8 mmol) of trifluoroacetic acid. An immediate deep red color appeared. After 3 hr the solution was quenched with sodium bicarbonate solution, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to leave 2-(*p*-nitrobenzyl)-1,3-dithiane (**13b**) as a yellow solid which was recrystallized from ethanol to give 1.70 g (85%) of **13b** as yellow crystals, mp 87–92°. The analytical sample, mp 91–92.5°, was obtained by recrystallization from ethanol: nmr ($CDCl_3$) δ 7.3–8.1 (AB q, 4, aromatic J = 9 Hz), 4.3 (t, 1, $HC(S-)_2CH_2$, J = 7 Hz), 3.1 (d, 2, $-CH_2C(S-)_2H$, J = 7 Hz), 2.8 (m, 4, SCH_2), 1.7–2.3 (m, 2, $CH_2CH_2CH_2$).

Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.48; S, 25.11. Found: C, 51.61; H, 5.33; N, 5.50; S, 24.94.

9c.—A procedure similar to that described above was followed to yield 2-(ferrocenylmethyl)-1,3-dithiane (64%) as golden crystals, mp 85–86.5° (from MeOH): nmr ($CDCl_3$) δ 4.1 (br s, 10, cyclopentadienyl and $HC(S-)_2CH_2$), 2.6–2.9 (m, 6, SCH_2 and Fc CH_2), 2 (m, 2, CH_2).

Anal. Calcd for $C_{15}H_{18}FeS_2$: C, 56.61; H, 5.70; S, 20.15; Fe, 17.55. Found: C, 56.40; H, 5.59; S, 20.27; Fe, 17.42.

Reactions of 6 with Electrophiles. Bromine.—Bromine (0.08 ml, 0.24 g, 1.46 mmol) was added to a solution of **6** (277 mg, 1.11 mmol) in 25 ml of carbon tetrachloride and the solution was stirred for 5 min. The solvent and excess Br_2 were removed under reduced pressure and the residue was placed on an alumina column and eluted successively with pentane, chloroform, and ether. The chloroform fractions yielded, on evaporation, 294 mg (81%) of **15a** as an orange syrup which crystallized readily and was homogeneous on tlc.

Recrystallization from methanol gave the analytical sample: mp 96–97°; nmr ($CDCl_3$) δ 7.45 (m, 5, aromatic), 3.45 (m, 2, SCH), 2.35–1.15 (m, 8, CH_2); mass spectrum (70 eV) m/e (rel intensity) 328 (100), 326 (99), 214 (50), 212 (49), 165 (32), 133 (43), 121 (63), 89 (54).

Anal. Calcd for $C_{14}H_{15}BrS_2$: C, 51.37; H, 4.62; Br, 24.41; S, 19.60. Found: C, 51.39; H, 4.83; Br, 24.06; S, 19.40.

***N*-Bromosuccinimide.**—A mixture of **6** (600 mg, 2.41 mmol) and *N*-bromosuccinimide (430 mg, 2.41 mmol) in 10 ml of carbon tetrachloride was stirred at 25° for 3 days. After filtration through Celite, the solvent was removed under reduced pressure and the residue was recrystallized from methylene chloride–hexane to afford 611 mg (78%) of **15a**, mp 95–96°, identified by ir and nmr.

A similar procedure but employing a 1.5-hr reflux yielded 75% of **15a**, mp 92–94°.

Pyridinium Bromide Perbromide.—To a solution of **6** (248 mg, 1.00 mmol) in 12 ml of acetic acid was added 320 mg (1.00 mmol) of pyridinium bromide perbromide and the solution was allowed to stand for 1 hr. Water (100 ml) was added and the solution was extracted with methylene chloride. The methylene chloride layer was washed (potassium carbonate solution), dried (Na_2SO_4), and evaporated to give 301 mg (92%) of crude **15a** which was recrystallized from hexane to yield 221 mg (67%) of **15a**, mp 90–92°, identified by ir.

***N*-Chlorosuccinimide.**—A mixture of **6** (248 mg, 1.00 mmol) and *N*-chlorosuccinimide (136 mg, 1.00 mmol) in 13 ml of CCl_4 was refluxed for 12 hr, cooled, filtered, and evaporated to leave crude **15b**, which was recrystallized from hexane to yield 144 mg (51%) of hexahydro-2-(α-chlorobenzylidene)-*trans*-1,3-benzodithiole (**15b**): mp 91–92°; nmr ($CDCl_3$) δ 7.47 (m, 5, aromatic), 3.40 (m, 2, SCH), and 2.50–1.10 (m, 8, CH_2); mass spectrum (70 eV) m/e (rel intensity) 284 (13), 282 (35), 178 (22), 170 (25), 168 (68), 133 (44), 124 (35), 121 (41), 89 (100), 81 (65).

Repeated recrystallization from methanol gave the analytical sample, mp 91–92°.

Anal. Calcd for $C_{14}H_{15}ClS_2$: C, 59.43; H, 5.35; Cl, 12.54; S, 22.68. Found: C, 59.56; H, 5.18; Cl, 12.65; S, 22.79.

Thiocyanogen.—Bromine (480 mg, 3.00 mmol) in 10 ml of carbon tetrachloride was added to a slurry of lead(II) thiocyanate[14] (970 mg, 3.00 mmol) in 25 ml of ethyl acetate in a foil-wrapped flask to protect from light. After 20 min the bromine had been consumed and 693 mg (2.80 mmol) of **6** in 10 ml of ethyl acetate was added and the reaction mixture was stirred overnight. The solution was filtered through Celite and evaporated, and the residue was recrystallized from methylene chloride–hexane to yield 705 mg (82%) of hexahydro-2-(α-thiocyanobenzylidene)-*trans*-1,3-benzodithiole (**15c**): mp 110–113°; nmr ($CDCl_3$) δ 7.37 (m, 5, aromatic), 3.45 (m, 2, SCH), and 2.40–1.10 (m, 8, CH_2); mass spectrum (70 eV) m/e (rel intensity) 305 (100), 191 (22), 149 (33), 121 (46), 89 (15), 81 (22), 78 (48).

The analytical sample was obtained by recrystallization from methylene chloride–hexane, mp 114.5–115°.

Anal. Calcd for $C_{15}H_{15}NS_3$: C, 58.98; H, 4.95; N, 4.59; S, 31.49. Found: C, 59.14; H, 4.88; N, 4.75; S, 31.50.

***p*-Nitrobenzenediazonium Fluoroborate.**—To a solution of **6** (248 mg, 1.0 mmol) in 10 ml of methylene chloride was added 237 mg (1.0 mmol) of *p*-nitrobenzenediazonium fluoroborate. After 1 min the solution became deep red. After 15 min solid sodium bicarbonate was added, and the solution was filtered through Celite and evaporated to leave 389 mg (98%) of red product which was recrystallized from methylene chloride–hexane to give 229 mg (58%) of hexahydro-2-[α(*p*-nitrophenyl)azo]-benzylidene]-*trans*-1,3-benzodithiole (**15f**): mp 185–186°; nmr ($CDCl_3$) δ 7.6–8.2 (AB q, 4, aromatic, J = 9 Hz), 7.4 (br s, 5, aromatic), 3.5 (br s, 2 SCH), 1.2–2.5 (methylene envelope, 8); mass spectrum (70 eV) m/e (rel intensity) 397 (10), 315 (100), 121 (28), 89 (8), 81 (7).

Anal. Calcd for $C_{20}H_{19}N_3S_2O_2$: C, 60.43; H, 4.82; N, 10.57; S, 16.13. Found: C, 60.24; H, 4.75; N, 10.63; S, 16.22.

2,4-Dinitrobenzenesulfenyl Chloride.—A solution containing 497 mg (2.00 mmol) of **6** and 469 mg (2.00 mmol) of 2,4-dinitrobenzenesulfenyl chloride was allowed to stand for 0.5 hr and worked up as in the preceding experiment to afford 626 mg (70%) of hexahydro-2-{α-[(2,4-dinitrophenyl)thio]benzylidene}-*trans*-1,3-benzodithiole (**15d**) as orange needles: mp 154.5–156°; nmr ($CDCl_3$) δ 7.6–9.1 (ABM pattern, 3, aromatic, J = 9 and 3 Hz), 7.2–7.6 (m, 5, aromatic), 3.5 (br m, 2, SCH), 1.3–2.5 (br m, 8, methylenes).

The analytical sample, mp 158–160°, was obtained by recrystallization from hexane–methylene chloride.

Anal. Calcd for $C_{20}H_{18}N_2O_4S_3$: C, 53.79; H, 4.06; N, 6.27; S, 21.54. Found: C, 53.60; H, 4.22; N, 6.29; S, 21.72.

Diethyl Azodicarboxylate.—A slight excess of diethyl azodicarboxylate was added to 500 mg (2.02 mmol) of **6** in 5 ml of methylene chloride and allowed to stand for 6 hr. After evaporation of the solvent the residue was recrystallized from methylene chloride–hexane to give 670 mg (79%) of diethyl [α-(hexahydro-*trans*-1,3-benzodithiol-2-ylidene)benzyl]bicarbamate (**15e**): mp 167–169°; nmr ($CDCl_3$) δ 7.42 (m, 5, aromatic), 6.86 (s, 1, NH), 4.17 (two t, 4, J = 6 Hz, OCH_2), 3.36 (br m, 2, SCH), 2.38–1.03 (m, containing two t at δ 1.21 and 1.19, J = 6 Hz, 14, CH_2 and CH_3).

Anal. Calcd for $C_{20}H_{26}N_2O_4S_2$: C, 56.84; H, 6.20; N, 6.63; S, 15.18. Found: C, 57.02; H, 6.19; N, 6.63; S, 15.31.

Chlorosulfonyl Isocyanate.—A solution containing 542 mg of **6** in 10 ml of methylene chloride was cooled in an ice-salt bath while 0.2 ml (2.2 mmol) of chlorosulfonyl isocyanate was added slowly. The solution was stirred for 0.5 hr, then neutralized (solid $NaHCO_3$), dried (Na_2SO_4), filtered through Celite, and evaporated to leave 803 mg of solid which was recrystallized from hexane–methylene chloride to afford 612 mg of product, mp 138–140°. Further recrystallization did not improve the melting point.

Anal. Calcd for $C_{15}H_{16}NO_3S_3Cl$: C, 46.20; H, 4.14; N, 3.59; S, 24.67; Cl, 9.09. Found: C, 44.06; H, 4.59; N, 3.38; S, 22.13; Cl, 7.91.

In another run the crude product was treated with 4 *N* sodium hydroxide solution with the expectation of characterizing the

(14) W. H. Gardner and H. Weinberger, *Inorg. Syn.*, **1**, 84 (1939).

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.

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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