Organic Disulfides and Related Substances. XXV. Thiocarbamoyl and Imidocarbamoyl Disulfides[1a-d]

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Thiolsulfonates (aryl, primary, or tertiary alkyl) thioalkylated dithiocarbamates (unsubstituted, N-methyl, N,N-dimethyl) to form unsymmetrical thiocarbamoyl disulfides in 48–88% yield; a promising synthesis of an ammonium alkanesulfinate resulted as a side issue. Dipotassium N-(*p*-toluenesulfonyl)dithiocarbamate was dialkylated at sulfur by methyl sulfate but only monothioalkylated by a thiolsulfonate. An imidocarbamoyl disulfide was prepared from a sulfenyl chloride with thiourea under milder conditions than used previously, which minimized disproportionation. Evidence that the products were unsymmetrical disulfides and not mixtures of symmetrical ones included independent synthesis, X-ray diffraction, thin layer chromatography, spectra, solubility properties, and thermal decomposition in solution. In the thermal decompositions, the N,N-dimethyl compounds were the most stable, the N-methyl next, and the unsubstituted least; the first of these disproportionated to symmetrical disulfides, the last underwent elimination (giving a trisulfide, carbon disulfide, and a mixture of ammonium thiocyanate with thiourea), and the N-methyl series did both. Within each class the order of decreasing stability was *t*-alkyl > primary alkyl > aryl; decomposition was fastest in solvents of highest polarity. Two disulfides were active as antiradiation drugs, and several had other useful biological properties.

Previous papers in this series have shown thiolsulfonates to be stable reagents which conveniently thioalkylate a wide variety of thiols to form unsymmetrical disulfides (for leading references, see 1a,b). This paper extends the thioalkylation to dithiocarbamates (eq 1).

$$\underset{\textbf{1–3}}{R_1R_2NC(S)S^-} + \underset{\textbf{4–6}}{R_4SO_2SR_3} \longrightarrow \underset{\textbf{7–15}}{R_1R_2NC(S)SSR_3} + R_4SO_2^- \quad (1)$$

1, R_1, R_2 = CH_3 — **4**, R_4 = p-$CH_3C_6H_4$; R_3 = $C(CH_3)_3$
2, R_1 = CH_3; R_2 = H — **5**, R_3, R_4 = p-$CH_3C_6H_4$
3, R_1, R_2 = H — **6**, R_3, R_4 = $AcNH(CH_2)_2$

The products, although properly named trithiopercarbamates, are unsymmetrical disulfides. Their disproportionation to symmetrical disulfides (eq 2) also is

$$2RSSR' \longrightarrow RSSR + R'SSR' \quad (2)$$

reported in order to extend clarifications of structural and electronic influences on disproportionation beyond situations considered in earlier papers of this series (for leading references, see 1a,b). A further reason for interest in the products was the possibility of several types of biological activity.

Trithiopercarbamates have been prepared hitherto by three general methods: by equilibration of two symmetrical disulfides;[2] by reaction of a sulfenyl chloride,[3] thiocyanate,[4] or sulfite[5] with a dithiocarbamate salt; and by oxidative coupling of dithiocarbamate and xanthate salts.[6] The trithiopercarbamates **7–15** prepared according to eq 1 are listed in Table I. The groups involved demonstrate generality for the new thioalkylation, in that aryl and either primary or tertiary alkyl groups could be used with unsubstituted, monosubstituted, or disubstituted dithiocarbamate salts; trial of secondary alkyl or other aryl thiolsulfonates seemed superfluous. The primary alkyl thiolsulfonate **6** also thioalkylated dipotassium N-(*p*-toluenesulfonyl)dithiocarbamate to give **16**. All yields were in the range of 48–88%.

In procedures A, B, and C for the preparations, the unsymmetrical disulfide was quickly removed from contact with the dithiocarbamate, either by its own precipitation or by extraction. This technique probably minimizes disproportionation of the unsymmetrical disulfide, since disproportionation doubtless would be catalyzed by unreacted dithiocarbamate ion (*cf.* ref 7). As an illustration of procedure A, **7** was prepared by stirring potassium N,N-dimethyldithiocarbamate (**1**) in water with *t*-butyl *p*-toluenethiolsulfonate (**4**) in ether; potassium *p*-toluenesulfinate and any excess **1** remained in the aqueous phase. The other *t*-butyl trithiopercarbamates (**10**, **13**) were prepared like **7** by procedure A, but from **2** or **3** with **4**.

Compound **7** has been reported before (*cf.* Table I). Since it seemed necessary to establish a typical structure rigorously, **7** was chosen in view of the difference in properties reported here and earlier.[3c] It was independently synthesized by the reaction of eq 3. The

$$(CH_3)_3CSCl + \underset{\textbf{1}}{(CH_3)_2NC(S)S^-} \longrightarrow \underset{\textbf{7}}{(CH_3)_2NC(S)SSC(CH_3)_3} \quad (3)$$

structure of **7** also was confirmed by X-ray diffraction.[8]

Procedure A was equally satisfactory for reactions of *p*-tolyl *p*-toluenethiolsulfonate (**5**), which thioalkylated **1–3** giving **9**, **12**, and **15**. Too long a reaction time was disadvantageous, since the yield of **9** dropped from 83 to 27% with 6 hr instead of 0.5 hr, and so was preparation in a homogeneous medium, since such an attempted preparation of **15** gave *p*-tolyl disulfide (86%).

Procedure B, with water as the only solvent, was developed for the water-soluble thiolsulfonate **6**; it

(1) (a) Paper XXIV: L. Field, H. K. Kim, and M. Bellas, *J. Med. Chem.*, **10**, 1166 (1967). (b) Paper XXIII: L. Field and J. D. Buckman, *J. Org. Chem.*, **32**, 3467 (1967). (c) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. We thank J. L. Richards for significant help in nmr aspects. (d) Abstracted from part of the Ph.D. Dissertation of J. D. B. (Vanderbilt University, June, 1966), which may be consulted for greater detail. (e) Du Pont Postgraduate Teaching Assistant, 1964–1965.

(2) M. Kleiman, U. S. Patents 2,610,967 and 2,610,968 (1952); *Chem. Abstr.*, **48**, 8812 (1954).

(3) For examples, see (a) J. P. Brown, British Patent 901,637 (1962); *Chem. Abstr.*, **57**, 12645 (1962); (b) H. L. Klopping, *J. Org. Chem.*, **26**, 1146 (1961); (c) W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).

(4) M. Hunt, U. S. Patent 2,390,713 (1945); *Chem. Abstr.*, **40**, 1875 (1946).

(5) A. A. Watson, *J. Chem. Soc.*, 2100 (1964).

(6) J. A. Lambrech and W. H. Hensley, U. S. Patent 2,843,518 (1958); *Chem. Abstr.*, **52**, 18999 (1958).

(7) *Cf.* L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966).

(8) Private communication from D. J. Mitchell. Tentative values of bond lengths, kindly provided by Dr. Mitchell, may be found in the Ph.D. Dissertation of J. D. B., pp 52, 53.[1d]

TABLE I
SYNTHESIS OF THIOCARBAMOYL DISULFIDES, $R_1R_2NC(S)SSR_3$

Compd	R_1	R_2	R_3	Time, hr, (procedure)[a]	Ratio[b]	Yield, % (mp, °C)[c]	Solvents[d]	Mp, pure, °C[e]	Anal. calcd (found), % C	H	N	S	Tlc R_f*[f]
7[g]	CH_3	CH_3	$(CH_3)_3C$	3(A)	1.1	82 (69–71)	M, C–P, P	70–71[e]	40.16 (40.18)	7.22 (7.25)	6.69 (6.67)	45.94 (45.92)	0.95[h]
8	CH_3	CH_3	$AcNH(CH_2)_2$	1(B)	1.0	71 (79–80)	Ct, Et, W	80–80.5	35.27 (35.06)	5.92 (5.93)	11.75 (11.98)	40.35 (40.23)	1.0[i]
9	CH_3	CH_3	p-$CH_3C_6H_4$	0.5(A)[j]	1.2	83 (83–86)	IPA, EO, M	88–88.5	49.35 (49.36)	5.39 (5.33)	5.76 (5.64)	39.52 (39.73)	0.81[i]
10	CH_3	H	$(CH_3)_3C$	5(A)[k]	1.5	59 (65–67)	M, IPA	66–67	36.88 (36.90)	6.71 (6.67)	7.18 (7.25)	49.23 (49.17)	0.98
11	CH_3	H	$AcNH(CH_2)_2$	0.8(B)[l]	1.0	83 (84–86)	M, C–EO, A–P	87–88	32.12 (32.06)	5.39 (5.66)	12.49 (12.41)	42.89 (42.76)	0.70
12	CH_3	H	p-$CH_3C_6H_4$	0.3 (A)	1.1	58 (84–87)	P, Hx, Hp, IPA	88–89	47.12 (47.08)	4.83 (4.80)	6.11 (5.98)	41.94 (41.91)	0.95[h]
13	H	H	$(CH_3)_3C$	3 (A)	2.0	68 (92–93)[m]	Cy, M, Hx	92–93	33.11 (33.10)	6.11 (5.92)	7.72 (7.90)	53.04 (52.90)	0.95
14	H	H	$AcNH(CH_2)_2$	(C)	1.0	76 (81–83)[n]	M–W (1:4)	95–96	28.55 (28.53)	4.68 (4.84)	13.31 (13.23)	45.74 (45.89)	0.79
15	H	H	p-$CH_3C_6H_4$	0.5 (A)[o]	1.0	88 (113–114)	A–Hx	114–114.5	44.62 (44.43)	4.24 (4.24)	6.50 (6.53)	44.67 (44.63)	0.22[i]
16	Ts[p]	H	$AcNH(CH_2)_2$	0.3	0.91	48 (93–94)	M–W (1:2), C–EO	99–100	39.59 (39.93)	4.42 (4.54)	7.69 (7.64)	35.18 (34.15)	0.55[h]
22[q]						55 (102–104)	t-BuOH	138–139[r]	47.14 (47.15)	4.52 (4.59)	7.86 (7.84)	26.99 (26.91)	0.72[h]

[a] Hours allowed for reaction; for procedures A, B, and C, see Experimental Section. [b] The molar ratio used of $R_1R_2CS_2^-/R_4SO_2SR_3$. [c] Yield of disulfides with the melting point reported, calculated on the basis of eq 1. [d] Solvents used for recrystallization to constant melting point: A, acetone; t-BuOH, t-butyl alcohol; C, chloroform; Ct, carbon tetrachloride; Cy, cyclohexane; EO, anhydrous ether; Et, absolute ethanol; Hp, heptane; Hx, hexane; IPA, isopropyl alcohol; M, methanol; P, pentane; W, distilled water. [e] Melting point of analytically pure disulfides. [f] See footnote 11 of reference 1b for details. [g] Disulfide 7 has been reported previously but only as material with bp 121° (0.7 mm).[3c] [h] Eastman chromagram sheet was used, Type K301R (silica gel). [i] 2-Propanol–water (9:1) for development. [j] Reaction complete after 0.5 hr. Reaction for 6 hr gave only 27% 9, which was separated from p-tolyl disulfide (48%) and tetramethylthiuram disulfide (36%) by recrystallization from IPA. [k] With a time of 3.5 hr and a ratio of 1.1, reaction was incomplete, and disulfide 10 could not be separated from the thiolsulfonate. [l] Disulfide 11 was obtained by cooling the reaction mixture to 5°, removing 11 which crystallized, and washing it with ice water (100 ml). [m] Melting point after one recrystallization from cyclohexane; the crude yield of 13 was 100%, mp 74–78°. [n] After one recrystallization from M–W, 62% yield of 14, mp 94–95°. [o] Attempted preparation of 15 by reaction of 3 and 5 in a homogeneous medium (IPA–W), essentially procedure B, resulted in p-tolyl disulfide (86% yield). [p] Ts = p-$CH_3C_6H_4SO_2$. [q] (Phenyldithio)formamidine p-toluenesulfonate; see Experimental Section for preparation. [r] Melting point tube immersed at 125°, then heated at 2°/min increase. The melting point varies with the rate of heating. It drops if 22 is exposed to air for several days.

should be appropriate for most thiolsulfonates soluble in water and only sparingly so in ether. Thioalkylations by 6 of the dimethyl- and methyldithiocarbamates (1 and 2) were done in fairly dilute aqueous solution, 8 and 11 (which separated) being subsequently extracted.

However, reaction of 6 with the dithiocarbamate 3 by procedure B gave the trisulfide 17 (56%), not the disulfide 14 (eq 4, paths a and b); formation of 17 might

$$\underset{3}{H_2NC(S)S^-NH_4^+} + \underset{6}{AcNH(CH_2)_2SO_2S(CH_2)_2NHAc} \xrightarrow{a}$$

$$\underset{18}{AcNH(CH_2)_2SO_2^-NH_4^+} + \underset{14}{[H_2NC(S)SS(CH_2)_2NHAc]} \xrightarrow{b}$$

$$\underset{17}{AcNH(CH_2)_2SSS(CH_2)_2NHAc} \quad (4)$$

occur through decomposition of 14 to the hydrodisulfide, $HSS(CH_2)_2NHAc$ (*vide infra*), which then is thioalkylated by 6 or 14. Use of nonaqueous solvents gave 14 (49% yield) but, more importantly, unexpectedly led to a useful preparation of the otherwise difficultly obtainable sulfinate salt 18 (82% yield); since thiolsulfonates are available by methods mentioned earlier in this series of papers, further attention to this route as a possible general synthesis of sulfinates seems worthwhile. The best preparation for 14 was procedure C, in which a minimum of water at 0° was used; doubling this volume reduced the yield of 14 from 76 to 37%.

In a study of the thioalkylation of dipotassium N-(*p*-toluenesulfonyl) dithiocarbamate (19) by either one *or* two molar proportions of the acetamido thiolsulfonate 6, the product (after acidification) was the monothioalkylated disulfide 16 of Table I. As shown by eq 6 therefore, the thiolsulfonate 6 attacks salt 19

$$\underset{19}{p\text{-}CH_3C_6H_4SO_2N{=}C(S^-K^+)_2} \xrightarrow{(CH_3O)_2SO_2}$$

$$\downarrow 6 \qquad \underset{21}{p\text{-}CH_3C_6H_4SO_2N{=}C(SCH_3)_2} \quad (5)$$

$$\underset{20}{p\text{-}CH_3C_6H_4SO_2N^-(K^+)C(S)SS(CH_2)_2NHAc} \xrightarrow{H^+}$$

$$\underset{16}{p\text{-}CH_3C_6H_4SO_2NHC(S)SS(CH_2)_2NHAc} \quad (6)$$

only once, not twice, forming the resonance-stabilized salt 20 (61–63%). This outcome contrasts markedly with that of dialkylation (with unspecified agents) which reportedly *can* occur with the salt 19 (eq 5).[9] The monopotassium salt 20 was still the major product isolated even when two molar proportions of thiolsulfonate 6 were employed in dimethylacetamide, which effects complete solution and thus precludes cessation of reaction simply because of precipitation of salt 20 (as occurred in the first-mentioned reactions with water as solvent).

Consistent with assignment of structure 20 to the salt were elemental analysis, facile hydrolysis to *p*-toluenesulfonamide (78% yield), and conversion into 2-acetamidoethyl N-(*p*-toluenesulfonyl)trithiopercarbamate (16). The ir spectra of salt 20 and of the protonated form 16 were essentially identical, except for a

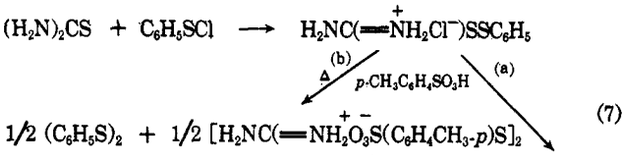
(9) R. Gompper and W. Hägele, *Chem. Ber.*, **99**, 2885 (1966).

new N–H absorption for **16** at 3190 cm^{-1}. This N–H absorption and also lack of S–H absorption at about 2550 cm^{-1} argue for assignment of the trithiopercarbamate structure to **16** (and hence to **20**) instead of the alternative iminethiol structure; furthermore, had the salt **20** been in the iminethiolate form, it probably could not have been recrystallized, because of the marked catalytic effect of thiols on disproportionation.[7]

In view of our results, it was important both to confirm the reported dialkylation[9] and to establish whether it involved S,S or S,N disubstitution. Dialkylation of **19** with methyl sulfate to give **21** did indeed occur (79% yield; eq 5). The structure of **21** was established by elemental analysis, molecular weight, and hydrolysis to *p*-toluenesulfonamide (not N-methyl *p*-toluenesulfonamide, which would have resulted had S,N dialkylation occurred); nmr and ir spectra were consistent with structure **21** (see Experimental Section).

The explanation for only monothioalkylation of **19** by the thiolsulfonate **6**, contrasted with dialkylation by methyl sulfate, probably is that the attacking moiety of the thiolsulfonate is much less electrophilic than that of methyl sulfate. Similar behavior occurs with weakly nucleophilic Grignard reagents of sulfones, which can be substituted twice by isocyanates and acid chlorides but only once by (less electrophilic) esters and nitriles.[10]

An imidocarbamoyl disulfide was prepared by reaction of benzenesulfenyl chloride with thiourea in formic acid. Phenyldithioformamidine was isolated as its *p*-toluenesulfonate salt **22** (eq 7, path a). Conditions for the reaction of the sulfenyl chloride with thiourea can be far milder (15 min, 15°) than those



(7)

of Kopylova and Freidlina, who seem to have used prolonged heating at 100° in preparing the picrate corresponding to **22**.[11] Indeed, with reaction conditions of 3.5 hr at about 100°, we isolated only the symmetrical disulfides (eq 7, path b). Consistent with **22** as the structure of the product was the isolation of phenyl disulfide in 91% yield after hydrolysis.

Homogeneity of the unsymmetrical thiocarbamoyl disulfides (**7–16**, **22**) was demonstrated by thin layer chromatography (tlc; *cf.* Table I). Only a single spot for each product confirmed that these products were not 1:1 mixtures of two symmetrical disulfides with the same elemental analysis, a point additionally clear from the total lack of any behavior in solvents suggesting a mixture of the two markedly different symmetrical disulfides. Disproportionation of the unsymmetrical to symmetrical disulfides, discussed below, further confirmed this point, as did the ir spectra (new bands absent in either symmetrical disulfide, absence of certain bands of the symmetrical disulfides).

All of the unsymmetrical disulfides (**7–16**, **22**) were crystalline solids and, as solids, were stable for a minimum of several months. Thermal stabilities in solution were investigated by heating them in dioxane at 100° for various periods. Table II shows the effects of varied substituents in order of the classes of di-, mono-, or unsubstituted trithiopercarbamates, and then in the order within each class of *t*-butyl, primary alkyl, and aryl groups. It is at once apparent that the relative stabilities decrease in this same order of classes, and then of groups within classes. That is, as classes, the N,N-dimethyl compounds (**7–9**) were most stable, the N-methyl compounds (**10–12**, **16**) were next, and the unsubstituted compounds (**13–15**) were least stable.

The N,N-dimethyltrithiopercarbamates **7–9** disproportionated, as usual, by the general eq 2 (specifically by eq 8, Table II), but their unsubstituted counterparts **13–15** underwent elimination that requires the moiety –HNC(S)SS– (eq 10, Table II). The N-monosubstituted compounds **10–12** and **16** underwent considerable elimination (eq 9, Table II), but isolation of the symmetrical disulfides showed involvement also of the usual disproportionation (eq 2). The stabilizing effect of two substituents on the nitrogen probably is best explained by its prevention of the elimination (eq 9 and 10), and the intermediate stability of the monosubstituted trithiopercarbamates by its suppression; the noteworthy similarity of **11** and **16** in disproportionation suggests that the CH_3 and p-$CH_3C_6H_4SO_2$ groups on nitrogen act principally to inhibit elimination and that their quite different electronic effects must be insulated from effect on the disulfide bond.

Within each of the three classes, as remarked, the *t*-butyl compound was the most stable (**7**, **10**, **13**), the primary alkyl was the next (**8**, **11**, **16**, **14**), and the aryl was the least stable (**9**, **12**, **15**). This order of stability, *i.e.*, *t*-alkyl > primary alkyl > aryl, accords with our observations in other classes.[12]

Replacement of the C=S moiety of a trithiopercarbamate, *p*-tolyl trithiopercarbamate (**15**), with a $C{=}NH_2^+$ moiety to give (phenyldithio)formamidine *p*-toluenesulfonate (**22**) caused a marked increase in thermal stability (in 3 hr, 90% decomposition for **15** but only 39% for **22**; an explanation is offered below).

The effect of solvent on thermal stabilities was large. Solvents of higher polarity accelerated decomposition, suggesting that these reactions (all of which were done in the dark) are heterolytic processes, as we concluded also for thermally induced disproportionation of other unsymmetrical disulfides.[7] Thus Table II shows that *t*-butyl N,N-dimethyltrithiopercarbamate (**7**) disproportionated in 72 hr to the extent of only 3% in dioxane but of 13% in ethanol, that 2-acetamidoethyl N,N-dimethyltrithiopercarbamate (**8**) decomposed to the extent of only 4% in 24 hr in dioxane but of 30% in only 3 hr in ethanol, and that decomposition (3 hr) of *p*-tolyl trithiopercarbamate (**15**) increased from 0 to 90% to 100% as the solvent was changed from heptane to dioxane to 95% ethanol.

(10) L. Field, J. E. Lawson, and J. W. McFarland, *J. Amer. Chem. Soc.*, **78**, 4389 (1956).

(11) B. V. Kopylova and R. Kh. Freidlina, *Dokl. Akad. Nauk SSSR*, **159**, 138 (1964); *Chem. Abstr.*, **62**, 3934 (1965).

(12) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).

TABLE II

THERMAL STABILITIES OF UNSYMMETRICAL DISULFIDES (100°)

Disubstituted: $2(CH_3)_2NC(S)SSR \longrightarrow [(CH_3)_2NC(S)S]_2$ (**23**) + $(RS)_2$ (8)

Compd	R	Time, hr (solvent)[a]	Disproportionation, %,[b] based on [(CH₃)₂NC(S)S]₂	Disproportionation, %,[b] based on (RS)₂	Disproportionation, %,[b] based on (CH₃)₂NC(S)SSR recovery	Av[c]
7	$(CH_3)_3C$	24		0[d]	0	0
		72		3[d]	2	3
		3 (EtOH)			0	0
		72 (EtOH)	9	16	14	13
8	$AcNH(CH_2)_2$	24	4			4
		3 (EtOH)	30			30
		3 (H_2O)	32			32
9	p-$CH_3C_6H_4$	24	15[e]	15	18	16
		3(EtOH)	47			47

Monosubstituted: $2CH_3NHC(S)SSR \longrightarrow RS_3R + CS_2 + (CH_3NH)_2CS$ (9)

Compd	R	Time, hr	Decomposition, %,[f] based on RS_3R	Decomposition, %,[f] based on CS_2[g]	Decomposition, %,[f] based on $(CH_3NH)_2CS$	Decomposition, %,[f] based on $CH_3NHC(S)SSR$ recovery	Av
10	$(CH_3)_3C$	24	0[d]			0	0
		72	(11)[d]	18[h]	9[i]	11	12
11	$AcNH(CH_2)_2$	24		39			39
16	$AcNH(CH_2)_2$ p-$CH_3C_6H_4SO_2$ for CH_3	24	42				42
12	p-$CH_3C_6H_4$	24	97	92[d]	94[i]	100	96

Unsubstituted: $2H_2NC(S)SSR \longrightarrow RS_3R + CS_2 + (H_2N)_2CS$(or NH_4SCN) (10)

Compd	R	Time, hr	Decomposition, %,[f] based on RS_3R	Decomposition, %,[f] based on CS_2[g]	Decomposition, %,[f] based on $(H_2N)_2CS$, NH_4SCN	Decomposition, %,[f] based on $H_2NC(S)SSR$ recovery	Av
13	$(CH_3)_3C$	24	[d]	27[i]	31	28	29
		72	[i]	35[i]	61	42	46
14	$AcNH(CH_2)_2$	24	68	109	84	79	85
15	p-$CH_3C_6H_4$	3 (Hp)				0	0
		3	89	88[d]		93	90
		3 (EtOH)	100				100
		24	96	100[d]	100	100	99
22	C_6H_5 $(:N^+H_2{-}O_3SC_6H_4CH_3$-$p$ for $:S)$	3	39				39

[a] Unless otherwise specified, the solvent was dioxane; EtOH is 95% ethanol; Hp is heptane. All experiments were done at 100° using 1.00 mmol of disulfide in 10 ml of solvent in a sealed ampoule protected from light, as described earlier.[1b] [b] According to eq 8, with calculations made using one of the equations: "Disproportionation, %" = (1.00 − millimoles of $(CH_3)_2NC(S)SSR$ recovered) × 100; or 2(millimoles of RS_2R or $[(CH_3)_2NC(S)S]_2$ isolated) × 100/1.00. [c] Numerical average of the other values listed. [d] Determined by glpc. *t*-Butyl disulfide and trisulfide were produced by decomposition of disulfide **10**, but only the disulfide was estimated quantitatively by glpc. Disulfide **13** decomposed to give *t*-butyl trisulfide as determined by qualitative glpc. [e] Determined by nmr. [f] According to eq 9 or 10 of Table II, with calculations as in footnote *b* except with RS_2R replaced by RS_3R, by CS_2, or by the thiourea. [g] The weight of carbon disulfide and other volatile products was determined by the difference from the theoretical weight after evaporation of solvent and drying. [h] Calculated by substituting (milligrams lost)/(millimole weight of CS_2 + millimole weight of *t*-Bu_2S_x (where $x = 2$) for RS_2R in the second equation of footnote *b*, Table II. [i] Identified by infrared spectrum and tlc. [j] $x = 3$ in footnote *h*, Table II.

As mentioned, the unsubstituted trithiopercarbamates **13–15** and the unsubstituted imidocarbamoyl disulfide **22** evidently undergo elimination reactions in decomposing. These lead to a symmetrical *tri*sulfide, carbon disulfide, and thiourea (mixed with its isomer, ammonium thiocyanate), as shown by eq 10 (Table II). The over-all reaction of eq 10 seems best regarded as proceeding by eq 11–14, for each of which analogies may be cited[13] and which when added give

$$H_2NC(S)SSR \longrightarrow HNCS + RSSH \quad (11)$$

$$RSSH + H_2NC(S)SSR \longrightarrow RS_3R + H_2NC(S)SH \quad (12)$$

$$H_2NC(S)SH \longrightarrow CS_2 + NH_3 \quad (13)$$

$$NH_3 + HNCS \longrightarrow NH_4SCN \longrightarrow (H_2N)_2CS \quad (14)$$

(13) (a) For eq 11, see E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, p 239. (b) For eq 12, see F. Sanger, *Nature*, **171**, 1025 (1953). (c) For eq 13, see R. Zahradník, *Chem. Listy*, **50**, 808 (1956); *Chem. Abstr.*, **50**, 10708 (1956). (d) For eq 14, see ref 13a, Vol. V, 1963, p 11 ff.

eq 10. Other reactions undoubtedly are involved also.[1d] It is worth pointing out that hydrogen sulfide never was noticed, thus eliminating certain possible reactions. The sequence suggested by eq 11–14 is supported by the stability of the imidocarbamoyl disulfide **22**. Thus in eq 11 heterolytic cleavage of the C–S bond into a hydrodisulfide should be slower for **22** than for the thiocarbamoyl counterpart (**15**), as was observed, because the generation of a second positive charge required of **22** for its reaction should be resisted (it might be added that the tolyl group of **15** may contribute somewhat to its stability relative to the phenyl compound **22**, as it does in disproportionation,[9] even though the reaction is one of elimination).

It was remarked above that the monosubstituted trithiopercarbamates probably decompose to a considerable extent by elimination (eq 9, Table II) but partly also by disproportionation (eq 2). For the monosubstituted trithiopercarbamates (**10–12**, **16**),

evidence is given in Table II or the Experimental Section for formation of at least one product from each of these four by eq 9 and also (except for **12**) by eq 2.

An alternative explanation for the products from unsubstituted and monosubstituted trithiopercarbamates might be that disproportionation to the symmetrical disulfides occurs, followed by transfer of sulfur to a disulfide from a thiuram disulfide or its decomposition products as illustrated by eq 15. To

$$2H_2NC(S)SSR \longrightarrow [H_2NC(S)S]_2 + (RS)_2 \longrightarrow [H_2NC(S)]_2S + (RS)_2S \quad (15)$$

test this possibility, *p*-tolyl and 2-acetamidoethyl disulfide were each heated with thiuram disulfide. *p*-Tolyl disulfide was recovered unchanged (59%), and other sulfides could not be crystallized. However, what seemed about equal amounts of di- and trisulfide were recovered when the 2-acetamidoethyl disulfide was used, suggesting that disproportionation followed by sulfur transfer may well play a role.

All of the products (**7–16, 22**) were attractive potential antiradiation drugs because "a number of dithiocarbamates have shown considerable merit as protective agents in mammals...".[14] Those also containing aminoethylthio moieties were additionally attractive for reasons outlined earlier.[15] The *t*-butyl N,N-dimethyl compound (**7**) was rated "good" at a dose level of 350–700 mg/kg; the *t*-butyl unsubstituted compound (**13**) was rated "good" at 350–700 mg/kg and "slight to fair" at 150–350 mg/kg; others were inactive or nearly so at dose levels in the range of less than 50 to 700 mg/kg (**22** not yet tested).[16] Several products also are promising for controlling growth of bacteria and fungi,[17] and a number offer significant promise in inhibiting the growth of *Histoplasma capsulatum*.[18]

Experimental Section[19]

Materials.—Potassium N,N-dimethyldithiocarbamate (**1**) and N-methyldithiocarbamate (**2**) were commercial aqueous solutions;[20] concentrations were determined by a reported method.[21] Ammonium dithiocarbamate (**3**) was prepared by adding gaseous ammonia to a solution of carbon disulfide in ethyl acetate at 10–15°; the precipitate was washed with absolute ethanol, dry ether, and pentane, and was dried briefly in air;[22] yield was 99%. Preparations were as reported in the literature for *t*-butyl *p*-toluenethiolsulfonate (**4**);[23] *p*-tolyl *p*-toluenethiolsulfonate (**5**);[24] 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**6**);[25] tetramethylthiuram disulfide (from oxidation of **1** with ammonium persulfate),[26] mp 155–155.5° (lit.[26] mp 143–145°); N,N′-dimethylthiuram disulfide (from iodine oxidation of **2**),[27] mp 95.5–100° dec (lit.[27] mp 101.5–102°); thiuram disulfide (by oxidation of a solution of **3** in the presence of 1 equiv of 0.45 *N* hydrochloric acid with 0.1 *N* iodine–potassium iodide solution),[22] mp 152–153° dec (lit.[28] mp 150–153° dec); and 1,3-dimethylthiourea (by heating methylamine and carbon disulfide in methanol),[29] mp 49–51°, (lit.[30] mp 49–51.5°). 2-Acetamidoethyl and *p*-tolyl and *t*-butyl trisulfide were obtained as before,[25] as was 2-acetamidoethyl disulfide.[15] Other materials either were commercial or are referenced below.

Synthesis of Unsymmetrical Disulfides (7–16, 22). General Comment.—Except for variations noted in Table I, procedures A (for **7, 9, 10, 12, 13,** and **15**), B (for **8** and **11**), and C (for **14**) were as illustrated below, where related work also is included. The preparations of **16** and **22** differed from these, however, and are described separately below. Unless otherwise stated, reactions were done at room temperature. Properties and analyses of products not given below appear in Table I.

Procedure A. *t*-Butyl N,N-Dimethyltrithiopercarbamate (7).—A solution of 24.4 g (0.10 mol) of *t*-butyl *p*-toluenethilosulfonate (**4**) in 250 ml of ether was stirred vigorously with one of 0.11 mol of potassium N,N-dimethyldithiocarbamate (**1**) in 200 ml of water for 3 hr. Completion of the reaction then was indicated by disappearance from the ether phase of the strong $-SO_2-$ infrared absorption (1150, 1340 cm^{-1}) characteristic of the thiolsulfonate **4**; this technique was used in all applications of procedure A. The aqueous layer then was extracted twice with ether (25 ml). The combined extracts were washed three times with water (50 ml), and then were dried, and evaporated. Residual **7** (21.0 g, 100%) was recrystallized from methanol (100 ml) with Dry Ice cooling to yield 17.10 g (82%), mp 69–71°.

For independent synthesis of **7**, a solution of 0.60 mol of potassium N,N-dimethyldithiocarbamate (**1**) in water (total volume, 150 ml) was added over 1 hr at 15–25° to a stirred solution of 2-methyl-2-propanesulfenyl chloride.[31] After 45 min more of stirring, precipitate was removed, washed with water, and recrystallized to yield 90 g (72%), mp 68–71°.

Procedure B. 2-Acetamidoethyl N,N-Dimethyltrithiopercarbamate (8).—A solution of 40.0 g (0.15 mol) of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**6**) in water (100 ml) was poured into one of 0.15 mol of the dithiocarbamate **1** in 40 ml of water. Yellow oil separated at once. After 1 hr, with occasional swirling, the mixture was extracted with five 50-ml portions of chloroform. The extracts were washed twice with 40-ml portions of 5% aqueous sodium bicarbonate at 0–5° and once each with 40 ml of 1 *N* hydrochloric acid and water. Drying and evaporation then gave an oil, which when rubbed with dry ether (0°) gave 25.2 g (71%) of **8**, mp 79–80°.

Attempted preparation of **14** by procedure B gave **2-acetamidoethyl trisulfide (17).** The thiolsulfonate **6** (20 mmol) in water (20 ml) was mixed with carbamate **3** (20 mmol) in water (20 ml) and the mixture was stirred for 15 min and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to an oil, which crystallized when rubbed with ether to give the trisulfide **17**, amounting after recrystallization to 1.50 g (56%), mp 94–95°; further recrystallization gave **17** with a constant melting point of 95–95.5° (lit.[25] mp 95–95.5°).

Procedure C. 2-Acetamidoethyl Trithiopercarbamate (14).—Ammonium dithiocarbamate (**3**, 2.75 g, 25 mmol) was added all at once to a solution of 6.70 g (25 mmol) of the acetamido thiolsulfonate **6** in 3 ml of water at 0° (prior warming was neces-

(14) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p 89.

(15) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(16) Private communication from Drs. D. P. Jacobus and T. R. Sweeney, Walter Reed Army Institute of Research. For details of testing and the scale of activity, see L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(17) J. D. Buckman, B. S. Johnson, and L. Field, *Can. J. Microbiol.*, **12**, 1263 (1966).

(18) I. McVeigh and Z. Evans, *Mycopathol. Mycol. Appl.*, in press.

(19) Melting points are corrected. For infrared absorptions: s = strong, unspecified = medium, w = weak, br = broad. Where identity of samples is mentioned, identity was proved by ir spectra and usually checked also by mixture melting point. Nmr spectra were obtained with a Varian Model A-60 spectrometer with tetramethylsilane as an internal standard; we thank the National Science Foundation for departmental Grant GP-1683 toward purchase of the instrument. Other details, such as for thin layer chromatography (tlc), gas–liquid partition chromatography (glpc), etc., were as described in footnote 11 of ref 1b (*cf.* also ref 1d).

(20) Kindly supplied by Buckman Laboratories, Inc., Memphis, Tenn.

(21) E. Kheraskova, E. Korsunskaya, and L. Veĭsbrut, *J. Rubber Ind. USSR*, 933 (1936); *Chem. Abstr.*, **31**, 2966 (1937).

(22) L. P. Miller, *Contrib. Boyce Thompson Inst.*, **5**, 29 (1933).

(23) T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).

(24) L. Field and T. F. Parsons, *ibid.*, **30**, 657 (1965).

(25) J. D. Buckman and L. Field, *ibid.*, **32**, 454 (1967).

(26) H. I. Cramer, U. S. Patent 2,014,353 (1935); *Chem. Zentr.*, **107**, 2227 (1936).

(27) A. D. Cummings and H. E. Simmons, *Ind. Eng. Chem.*, **20**, 1173 (1928).

(28) M. Freund and G. Bachrach, *Ann.*, **285**, 201 (1895).

(29) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol V, Chemical Publishing Co., Inc., New York, N. Y., 1963, p 43.

(30) O. Hecht, *Ber.*, **23**, 281 (1890).

(31) From addition of 0.32 mol of chlorine to 0.30 mol of *t*-butyl disulfide in 750 ml of pentane during 45 min at 28–31°.[30] Stirring was continued for 0.5 hr before **1** was added.

sary for dissolution of **6**). An oil, which separated at once, solidified when triturated in the still-chilled mixture for 0.5 hr. The solid then was washed with three 3-ml portions of ice–water by decantation to yield 3.95 g (76%) of **14**, mp 81–83°. When twice the volume of water was used, the yield of **14** was 37%, mp 85–86°.

Reaction of **6** with **3** in dioxane gave a useful synthesis of **ammonium 2-acetamidoethanesulfinate (18)**. A slurry of **6** (13.40 g, 50 mmol) and **3** (5.50 g, 50 mmol) in dioxane (70 ml) was stirred for 1 hr. The insoluble material was removed and washed with dioxane, 1-butanol, and chloroform to give 6.90 g (82%) of **18**, mp 163–165°.[32] Recrystallization from 95% ethanol–ether and methanol gave **18** with a constant melting point of 167–168.5° (immersion at 150°, temperature rise then of 2°/min) and ir absorption at 2800–3400 (s, br), 2000, 1640 (s), 1570, and 1040 cm^{-1}.

Anal. Calcd for $C_4H_{12}N_2O_3S$: C, 28.57; H, 7.19; N, 16.66; S, 19.11. Found: C, 28.20; H, 7.09; N, 16.50; S, 18.79.

Addition of ether to the combined dioxane filtrates, followed by chilling, gave 5.10 g (49%) of disulfide **14**, mp 83–84°, but only after repeated recrystallization could there be obtained **14** with mp 95–96° (2.94 g, 28%).

2-Acetamidoethyl N-(*p*-Toluenesulfonyl)trithiopercarbamate (16).—Dipotassium N-(*p*-Toluenesulfonyl)dithiocarbamate (19) was prepared, in a modification of the reported procedure,[9] by stirring 0.4 mol of potassium hydroxide, 0.2 mol of carbon disulfide, and 0.2 mol of *p*-toluenesulfonamide in 200 ml of N,N-dimethylformamide at 0° for 3.5 hr; dioxane (200 ml) was added, and precipitate was washed with dioxane (250 ml) and ether (1 l.) and dried under vacuum to yield **19**, (65–69%) as a hygroscopic powder. This was stored under dry nitrogen. Ir absorptions (Nujol mull) were at 1650, 1250–1300 (s, b), 1130, 1080, 970, 810, 680, and 560 cm^{-1}.

A solution of 29.5 g (0.11 mol) of thiolsulfonate **6** in water (100 ml) was added to 34.2 g (0.11 mol) of salt **19**. The resulting solution was stirred for 15 min. The potassium salt **20** precipitated. Water (100 ml) was added, and the salt **20** was separated and dried under vacuum over phosphorus pentoxide; the yield of potassium 2-acetamidoethyl N-(*p*-toluenesulfonyl)trithiopercarbamate (**20**) was 28.02 g (63%), mp 154–156° dec. Recrystallization (1:2 methanol–chloroform, 1:2 acetone–chloroform) gave **20** with a constant melting point of 165–166° dec; ir absorption (KBr) at 3400, 1650, 1530, 1410, 1310, 1180, 960, 815, and 660 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}KN_2O_3S_4$: C, 35.81; H, 3.76. Found: C, 36.02; H, 3.79.

Acidification of the filtrate to pH 2 with concentrated hydrochloric acid (2 ml), extraction with methylene chloride, evaporation of the extracts, and trituration of the oil left with cold dry ether gave 3.20 g (8%) of **16**, mp 91–92°. The infrared spectrum of **16** is essentially identical with that of salt **20** except for a new (NH) absorption at 3190 cm^{-1}.

Acidification of the slurry of salt **20**, prepared much as described above, with 1 equiv of 0.45 *N* acid, extraction, and addition of ether to the methylene chloride extract with Dry Ice cooling gave the disulfide **16** (mp 93–94°) in an over-all 48% yield from **19**.

Use of a 2:1 molar ratio of thiolsulfonate **6** to salt **19** in a procedure like the above gave **20** in 61% yield, mp 153–157° dec; with dimethylacetamide as solvent and a 2:1 ratio, the yield of **20** was only 32% (mp 155–162° dec; isolated by adding ether), but no indication could be found of dialkylation.

Hydrolysis of salt **20** was achieved by heating 121.1 mg (0.301 mmol) in water (3 ml) on a steam bath for 5 hr (more water being added to maintain the volume). Chilling and filtration gave 40.3 mg (78%) of somewhat impure *p*-toluenesulfonamide, mp 121–122°.

S,S'-Dimethyl-N-(*p*-toluenesulfonyl)imidodithiocarbonate (21).—A slurry of salt **19** (5.77 g, 17.9 mmol) and dimethyl sulfate (4.55 g, 36.0 mmol) in dimethylacetamide (25 ml) was stirred under nitrogen for 15 min. The mixture then was poured onto ice (150 g); the yield of insoluble **21** was 3.88 g (79%), mp 107–109°. Recrystallizations (methanol) gave **21** with a constant melting point of 110.5–111° (lit.[8] mp 109°); ir (Nujol), 1600, 1300, 1150, 1090, 925, 830, 810, 660, 560, and 530 cm^{-1}. This sample of **21** was identical with one prepared as described earlier[9] (89% yield, mp 101–104°), after purification of the latter.

Anal. Calcd for $C_{10}H_{13}NO_2S_3$: C, 43.61; H, 4.75; mol wt, 275. Found: C, 43.33; H, 4.70; mol wt (benzene), 283.

The nmr spectrum of **21** (10% solution in deuteriochloroform) showed the presence of 13 protons, with the four aromatic protons as a quartet at τ 2.04–2.77. The other nine protons were sharp singlets at τ 7.49 (6 H) and 7.58 (3 H); although one $-SCH_3$ could be represented in each of these peaks (the arylmethyl being coincident with one of them), since the 6 H peak is sharp, conceivably protons of the two $-SCH_3$ groups alone comprise the 6 H peak (the SCH_3 groups then being presumed magnetically equivalent because of rapid interconversion).

To substantiate the structure of **21**, 0.989 g (3.59 mmol) in 5 ml of 20% w/v potassium hydroxide in ethylene glycol was heated at 155–160° for 3 hr. Cooling, acidification, and chilling gave 0.185 g (30%) of *p*-toluenesulfonamide, mp 130–132°.

(Phenyldithio)formamidine *p*-Toluenesulfonate (22).—Chlorine (3.54 g, 50 mmol) was passed into a stirred slurry of 10.91 g (50 mmol) of phenyl disulfide in 85% formic acid (25 ml) at −10 to −5°. The solution of benzenesulfenyl chloride was left to warm to 15°, 3.81 g (50 mmol) of thiourea was added, and the mixture was stirred for 15 min. Solid was removed, and then *p*-toluenesulfonic acid monohydrate (9.50 g, 50 mmol) and ether (100 ml) were added to the filtrate. Chilling gave 3.03 g (17%) of **22**, mp 135–140°. Addition of more ether (100 ml) and chilling gave 6.80 g more of **22**, mp 102–104° (total yield, 55%).

Hydrolysis was consistent with the assigned structure; thus **22** (231.1 mg, 0.649 mmol) was heated under reflux in 10% aqueous sodium hydroxide (25 ml) for 2 hr. Extraction with pentane separated 64.7 mg (91%) of phenyl disulfide, mp 57–59°.

A similar reaction of benzenesulfenyl chloride and thiourea, but with heating of the formic acid under reflux for 3.5 hr, gave phenyl disulfide in 53% yield. Isolation as for **22** above then gave presumed formamidine disulfide di-*p*-toluenesulfonate (53%); recrystallization (ethanol, methanol) gave the presumed formamidine salt with a constant melting point of 174–175° dec, but analysis showed it to be still impure.

Anal. Calcd for $C_{16}H_{22}N_4O_6S_4$: C, 38.86; H, 4.48. Found: C, 39.68; H, 5.02.

Thermal Stabilities.—Dioxane solutions of the thiocarbamoyl disulfides **7–16** and the imidocarbamoyl disulfide **22** were heated at 100°, except where otherwise stated, all as described earlier (*cf.* footnote *a*, Table II).[1b] The extent of decomposition was determined using three methods, often each being used as a check on the others when feasible: "large-scale" isolation, nmr spectroscopy, and glpc. When possible, all products were separated and identified. Results are given in Table II, where values not referenced to nmr or glpc were obtained by "large-scale isolation."

A. "Large-Scale" Isolation.—Products left after removal of solvent from the reaction mixtures were separated by washing with appropriate solvents, as described next for various classes of disulfides. Materials separated were identified routinely by infrared spectra, melting point, and mixture melting point.

***p*-Tolyl Trithiopercarbamates (9, 12, 15).**—Washing the products with 5 ml of pentane at 0° removed *p*-tolyl di- or trisulfide. Evaporation then gave *p*-tolyl disulfide from **9** and *p*-tolyl trisulfide from **12** and **15**. Washing the pentane-insoluble residue with hot hexane (25 ml) removed unchanged unsymmetrical disulfide. The hexane-insoluble material then was identified as tetramethylthiuram disulfide from **9**, 1,3-dimethylthiourea from **12**,[33] and a mixture of ammonium thiocyanate and thiourea from **15** (that these comprised the mixture was shown by the infrared spectrum, water solubility, and a typical thiocyanate color with ferric chloride).

***t*-Butyl Trithiopercarbamates (7, 10, 13).**—The symmetrical *t*-butyl di- and trisulfide and carbon disulfide were identified and determined either by glpc (*vide infra*) or were estimated by weight loss (the sulfides, as well as carbon disulfide, were included in the weight loss for **10** and **13**; *cf.* footnotes *g*, *h*, and *j* of Table II). Hot hexane (10 ml) with the reaction products then dissolved unchanged **7**, **10**, or **13**, leaving the thiuram disulfide, the thiourea, or the thiourea–thiocyanate mixture undissolved.

(32) Essentially the same result was obtained with methanol or N,N-dimethylformamide instead of dioxane. To show that **18** was not the sulfonate salt, authentic **ammonium 2-acetamidoethanesulfonate (24)** was prepared by neutralizing a methanol suspension of the sulfonic acid[15] with gaseous ammonia. Ether then precipitated the sulfonate salt **24** with mp 179–181° (depressed to 152–161° by **18**); it had strong infrared absorptions at 1150–1220 cm^{-1} which **18** lacked.

(33) Crystalline dimethylthiourea was not obtained; hence this material was identified by comparison with authentic material of its infrared spectrum and tlc R_f* of 0.85.

2-Acetamidoethyl Trithiopercarbamates (8, 11, 14, 16).—Washing of the products from **8** with cold water removed **8** and 2-acetamidoethyl disulfide from tetramethylthiuram disulfide, which then could be identified. Washing the products from **11** with various solvents failed to give any separation; so these products were tentatively identified by tlc as 2-acetamidoethyl disulfide, 2-acetamidoethyl trisulfide (**17**), dimethylthiourea, unchanged disulfide **11**, and N,N'-dimethylthiuram disulfide, with R_f* 0.27, 0.38, 0.85, 0.79, and 0.90, respectively, by running authentic samples simultaneously on the tlc plate. Washing the products from disulfide **14** with chloroform (5 ml, 0°) dissolved the trisulfide **17**, leaving unreacted **14** and a thiourea–ammonium thiocyanate mixture; the mixture was separated from **14** by extracting it into 2 ml of ice–water. Washing the products from disulfide **16** with ice–water (5 ml) dissolved the 2-acetamidoethyl di- and trisulfide (**17**), leaving **16** and other products; the di- and trisulfide mixture was identified *via* ir spectrum and tlc; since the proportions of di- and trisulfide from **16** are unknown, the value of 42% for decomposition of **16** given in Table II reflects total reaction *via* both eq 9 and 2 but was calculated assuming only eq 2.

(Phenyldithioformamidine) *p*-Toluenesulfonate (22).—The reaction products were washed with hot hexane to give phenyl trisulfide. The trisulfide was identified by similarity of its infrared spectrum to that of *p*-tolyl trisulfide[25] (and its difference from that of the disulfide), especially in the region of 300–600 cm^{-1}, and by its melting point of 10–30° (lit. phenyl trisulfide mp 30°;[34] phenyl disulfide mp 59–60° [23]).

B. Use of Nmr.—The nmr spectra of tetramethylthiuram disulfide (**23**) and of *p*-tolyl N,N-dimethyltrithiopercarbamate (**9**) showed the N-methyl protons as distinct peaks at τ 6.42 and 6.53, respectively. Approximate correlation of these peak areas with concentrations of **23** and **9** were shown by the fact that a solution of tetramethylthiuram disulfide (**23**, 0.228 mmol, 57 mol%) and 0.170 mmol of **9** in 0.5 ml of chloroform had peaks at τ 6.42 and 6.53 with relative areas of 21.0 (**23**) and 4.80 (**9**). The mole % of **23** was 69% by the equation

mole % of **23** =
(0.5 area for **23**)(100)/(0.5 area for **23**) + (area for **9**)

A 4-ml aliquot of a 0.10 *M* solution of **9** in dioxane was heated for 24 hr at 100° and then was freeze dried (0.0974 g, 100% recovery). The residue, dissolved in 0.5 ml of chloroform, gave, by nmr spectroscopy, integrated areas for the N-methyl protons of **23** of 5.00 and for **9** of 28.50. This result indicates 15% disproportionation of **9** by the equation

disproportionation, %, =
(area for **23**) (100)/(area for **23**) + (area for **9**)

Attempts to use nmr spectra in other of the decomposition studies were unpromising.

(34) A. Baroni, *Atti Accad. Nazl. Lincei, Rend. Classe Sci. Fis., Mat., Nat.*, **11**, 579 (1930); *Chem. Abstr.*, **24**, 4771 (1930).

C. Use of Glpc.—Glpc was performed as usual (*cf.* ref 19), with an oven temperature of 135° for analysis of *t*-butyl sulfides and of 27° for carbon disulfide. Retention times at 135° follow: dioxane, 12–22 sec; *t*-butyl disulfide, 73 sec; 1,2,4-trichlorobenzene, 103 sec; *t*-butyl trisulfide, 195 sec. At 27°, they were 57 sec, carbon disulfide, and 250 sec, dioxane. A reference plot was prepared by dissolving various weights of *t*-butyl disulfide or carbon disulfide in 10 ml of dioxane. Aliquots of a standard solution of 1,2,4-trichlorobenzene were added (to assure a constant injection volume), and five 4-μl samples of each concentration were injected into the column; the resultant averaged peak heights plotted *vs.* the weight of disulfide gave linear plots passing through the origin; *t*-butyl trisulfide was not quantitatively determined in any experiments.

With **7**, **10**, and **13**, after the decomposition period noted in Table II, 1.0 ml of the chlorobenzene standard was added to the reaction solution, the contents were analyzed by the above procedure, and composition was determined from the standard plot (solutions of **7**, **10**, and **13**, with or without the chlorobenzene or *t*-butyl disulfide, showed no formation of *t*-butyl disulfide when tested directly). The reaction mixture remaining was analyzed as described in part A. *t*-Butyl disulfide was the only volatile product from disproportionation of disulfide **7**. *t*-Butyl trisulfide was the only volatile product from the decomposition of disulfide **13**. Disulfide **10** gave a mixture of *t*-butyl disulfide and trisulfide.

With **12** and **15** (only), after the times in Table II, the mixtures were analyzed for CS_2 by glpc, the amount being determined from the standard plot and the identity by noting peak enhancement upon addition of CS_2. In these decompositions, 1.0 *M* solutions of tolyl disulfides **12** and **15** in dioxane were used to enable determination of the carbon disulfide.

Decomposition of Thiuram Disulfide in the Presence of *p*-Tolyl or of 2-Acetamidoethyl Disulfide.—Solutions of *p*-tolyl or of 2-acetamidoethyl disulfide were heated with thiuram disulfide (one molar proportion of each) under reflux for 1 hr in 95% ethanol. The disulfide–trisulfide mixtures were isolated by evaporating the reaction mixtures and washing the residues with chloroform. *p*-Tolyl disulfide was recovered in 59% yield by recrystallization from 2-propanol; no other products could be crystallized. Tlc analysis of the products from 2-acetamidoethyl disulfide suggested that the disulfide and trisulfide were present in roughly equal amounts; much the same result occurred when the proportion of thiuram disulfide was increased fourfold.

Registry No.—**7**, 3304-97-0; **8**, 10048-08-5; **9**, 10048-05-2; **10**, 10048-09-6; **11**, 10048-07-4; **12**, 10048-06-3; **13**, 10048-10-9; **14**, 10090-39-8; **15**, 14259-42-8; **16**, 17396-86-0; **17**, 10325-48-1; **18**, 17396-88-2; **20**, 17396-90-6; **21**, 2651-15-2; **22**, 17414-35-6.