in the 1300- to 1350-cm^{-1} and 1140- to 1160-cm^{-1} regions. All aminovinyl sulfones exhibit, in addition to the characteristic sulfone bands which are shifted to slightly longer wavelengths, rather strong olefinic absorption in the 1570- to 1640-cm^{-1} region. All the aminoacrylate esters display a strong carbonyl absorption at *ca.* 1670 cm^{-1} in addition to strong olefinic absorption in the 1580- to 1590-cm^{-1} region.

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Organic Disulfides and Related Substances. XVIII. Synthesis and Disproportionation of 2-(Aryldithio)ethylamine Hydrochlorides[1a,b]

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Synthesis was achieved of unsymmetrical disulfides of the structure p-$XC_6H_4SS(CH_2)_2NH_3^+Cl^-$, both to permit evaluation for protection against ionizing radiation and clarification of factors which influence disproportionation of this model class of unsymmetrical disulfides. Thermally induced disproportionation in water, where X = H in the unsymmetrical disulfide, was accelerated by strong acid, alkali, or a thiol, and was inhibited by dilute acid. Kinetics of the series showed first-order dependence on the unsymmetrical disulfide, with an activation energy of 22.6 kcal/mole. There was good correlation of rates with Hammett σ constants (ρ = 1.9). Steric effects were negligible in an *ortho*-substituted analog, and the order of increasing resistance to thermally induced disproportionation was $NO_2 \ll Cl < H < CH_3 \lesssim CH_3O \lesssim 2,4,6\text{-}(i\text{-}C_3H_7)_3$. Acrylamide was not polymerized during the disproportionation. Photochemically induced disproportionation resulted essentially in inversion of the order of resistance, and acrylamide then was polymerized. Evidently the thermal process is largely heterolytic and the photochemical one largely homolytic. The thermally less stable disulfides often were easier to purify than the thermally more stable ones, because of their greater resistance to the destructive effects of even diffuse light.

The chemistry of unsymmetrical disulfides is of interest and significance synthetically and mechanistically, as well as in areas such as biochemistry (*e.g.*, protein cross linking, denaturation), industrial chemistry (*e.g.*, vulcanization), and polymer chemistry (*e.g.*, initiation, chain transfer, polysulfide polymers).[2] Another basis of interest, that of antiradiation drugs, was outlined earlier for 2-(aryldithio)ethylamine derivatives of type **1**.[3]

$$p\text{-}XC_6H_4SS(CH_2)_2NH_3^+Cl^- \xrightarrow{\Delta \text{ or } h\nu} 0.5(XC_6H_4S)_2 + 0.5[Cl^-H_3N^+(CH_2)_2S]_2 \quad (1)$$

(**1**; $-Cl^-H_3N^+(CH_2)_2SO_2H$)

$$p\text{-}XC_6H_4SH + Cl^-H_3N^+(CH_2)_2SO_2S(CH_2)_2NH_3^+Cl^-$$

(**2**)

Unsymmetrical disulfides of structure **1** afford a valuable tool for studying disproportionation to the symmetrical disulfides (eq 1). When the reaction is performed in water, the symmetrical aryl disulfide is the only sparingly soluble component of the mixture, and the reaction can be followed by its isolation. Disproportionation ordinarily is reversible and leads to an equilibrium mixture. However, with disulfides like **1** (at least where X = H[1b]), sparing solubility of the aryl disulfide forces the reaction to completion with no indication of reversibility. Capitalizing on the easy isolation of the aryl disulfide, we previously qualitatively correlated resistance to disproportionation with various structural features.[1b,3-5] This paper clarifies in more detail the nature of the disproportionation and factors which can influence it, with disulfides of type **1** as models.

Synthesis of disulfides **3–7**, shown in Table I, was done much as described earlier (eq 1),[6] except that after reaction of the thiol with thiosulfonate **2** unreacted thiol was extracted, after which **1** was converted to its free base. Since some products could not be recrystallized (facile disproportionation) this method minimized presence of a symmetrical disulfide which might be formed by attack of excess thiol. After formation of the free base by neutralization, it was extracted and then reconverted to its hydrochloride. Except for analogous *ortho*-substituted compounds, where disproportionation also was a problem,[1b] unreacted thiol usually has not been removed before neutralization; its further reaction during work-up of reaction mixtures undoubtedly resulted previously in conversions generally higher than those of Table I.[7] 2-(2,4,6-Triisopropylphenyldithio)ethylamine hydrochloride (**8**) was prepared using mercaptoethylamine and the aromatic thiolsulfonate.[7]

Purity of products **3–8** resulted from retention of by-product sulfinic acid as its salt in the aqueous layer after neutralization and from retention of disproportionation products either in the organic layer (XArS-SArX), when it was treated with acid, or in the acid layer (cystamine dihydrochloride) from which the desired product precipitated. Evidence of purity was that **3–8** showed no haziness when dissolved in water, a method proved with **4** to reveal as little as 0.5%

(1) (a) 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. Abstracted from part of the Ph.D. dissertation of T. F. P., Vanderbilt University, May 1964; (b) paper XVII: L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966); (c) DuPont Postgraduate Teaching Assistant, 1962–1963.

(2) For leading references see A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

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

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

(5) R. R. Crenshaw and L. Field, *ibid.*, **30**, 175 (1965).

(6) For leading references, see ref 7.

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

TABLE I

SYNTHESIS OF 2-(ARYLDITHIO)ETHYLAMINE HYDROCHLORIDES, p-$XC_6H_4SS(CH_2)_2NH_3^+Cl^-$

Compd	X	Mp, °C	Conversion, %	Thiol recovery, %	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found
3[a]	NO_2	187–189	46	8[b]	36.01	35.98	4.15	4.12	10.48	10.48	24.05	24.20
4[c]	H	132–133.5	55[c]		43.30	43.38	5.45	5.43	6.32	6.16	28.90	29.10
5	Cl	162–164	17	56	37.55	37.54	4.33	4.36	5.50	5.38	25.02	24.84
6	CH_3	133–135[d]	40	57								
7	CH_3O	149–150	37	47	42.92	42.82	5.62	5.54	5.57	5.51	25.45	25.37

[a] Since **3** was relatively easy to handle, unreacted thiol was not extracted. Chloroform was used to extract the free base. [b] Represents p-nitrophenyl disulfide formed by disproportionation of **3** during extraction of the free base; it formed a solid interface between layers. [c] For the reaction, the solvent was chloroform–methanol–water (200:50:10 ml) and the time was 2 hr. Unreacted thiol was not removed because **4** was relatively easy to handle; **4** was obtained by concentrating the acid extract of the free base (92% conversion). The **4** reported was analytically pure and was obtained by recrystallization from ethanol. [d] Lit.[3] mp 136–137°.

of phenyl disulfide;[1b] furthermore, *ortho* analogs showed only one spot in thin layer chromatography.[1b]

Disulfides **3–8** proved to be inactive for protection of mice against lethal effects of ionizing radiation.[8]

Depending on reaction conditions, and doubtless also on the structure, disproportionation of disulfides can be homolytic, heterolytic, or some combination of the two.[9] That homolysis of disulfides can be induced photochemically is exemplified by work of Kharasch and co-workers[10] and is assured by conversion of phenyl disulfide to benzenesulfenyl radicals.[11] Cole quite reasonably attributed to homolysis the redistribution of disulfides which he found to occur even in diffuse light (but not in its absence).[12] Leandri and Tundo concluded that disproportionation was homolytic; they irradiated *and* heated their disulfides, however,[13] and in view of results below heterolysis also may have been involved. Heterolysis, on the other hand, seems probable for disproportionation in sulfuric acid[14] or for disproportionation catalyzed by other electrophilic agents or by "S-nucleophiles."[2] Indeed, Schöberl and Gräfje concluded that certain disproportionations were heterolytic even though they were induced photochemically.[15] Both homolysis and heterolysis evidently can occur for methyl ethyl disulfide, which slowly disproportionates in the dark at room temperature (heterolysis) but induces polymerization of acrylonitrile only in light (homolysis),[16] as well as for methyl butyl disulfide, which disproportionates under influences as diverse as light, sodium sulfide, or hydrogen iodide.[17]

In studying disproportionation of disulfides of structure **1**, we first explored factors which seemed likely to influence the disproportionation by working with the typical phenyl compound **4**. Table II shows

TABLE II

INFLUENCES ON THE DISPROPORTIONATION OF 2-(PHENYLDITHIO)ETHYLAMINE HYDROCHLORIDE (**4**, 0.05 M) AT 68°

Expt	Conditions	Disproportionation, % 10 hr	Disproportionation, % 15 hr
1	Flash shielded by oil and foil	11	15
2	Flask shielded only by oil	14	18
3	Ambient (diffuse) light	53	87
4	Ultraviolet light[a]	104	105
5	Oxygenated	11	13
6	Degassed with nitrogen	13	16
7	Solvent, 2 M hydrochloric acid	65	68
8	After neutralization of **4** to free base	*b*	*b*
9	Solvent, 0.1 M hydrochloric acid	6	8
10	Solvent, 1 M aqueous potassium hydroxide	57[c]	26[c]
11	Solvent, 95% ethanol	9	14
12	Solvent, 1 M aqueous sodium chloride	43	63
13	Presence of 10 mole % of mercaptoethylamine hydrochloride	100	102
14	Presence of 15 mole % of ethylenediamine	92	100

[a] Hanovia lamp (100-w, Engelhard Industries Inc., Newark, N. J.) 6 in. from flask. [b] After 3 hr phenyl disulfide was isolated in 104% yield. [c] After 3 hr phenyl disulfide was isolated in 74% yield.

results in the disproportionation of **4** to phenyl disulfide and cystamine dihydrochloride, in aqueous solutions unless otherwise stated. Experiment 1 is a reference point for all other experiments. Experiment 2 suggests the desirability of careful shielding, a conclusion emphasized by the effects of laboratory light (expt 3) and of ultraviolet light (expt 4). Oxygenation had little effect (expt 5), so that degassing ordinarily was not used (confirmed by expt 6). Strong acid increased disproportionation (expt 7), again showing that disproportionation can be catalyzed by acid.[18] The free base of **4** is *extremely* unstable (expt 8), a general conclusion reached earlier.[4,5] Not surprisingly, dilute acid (not strong enough to catalyze sulfur–sulfur cleavage but strong enough to retain more free base of **4** as its salt) decreased disproportionation (expt 9). In view of the instability of the free base of **4**, it is not surprising that strongly alkaline conditions caused rapid disproportionation (expt 10); Table II suggests that disproportionation was only 57% in 10 hr and 26% in 15 hr, but the higher value (74%) after 3 hr shows that the low values were caused by conversion of phenyl disulfide to water-soluble materials by the alkali; the effect of alkali suggests that attack of hydroxyl ion may have played a role both in expt 10

(8) Results furnished through the kindness of Doctors D. P. Jacobus, T. R. Sweeney, and P. Coad of the Walter Reed Army Institute of Research. General procedures are described by L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(9) Only a few directly pertinent references can be cited here. The general subject of sulfur–sulfur scission is well reviewed in ref 2.

(10) M. S. Kharasch, W. Nudenberg, and T. H. Meltzer, *J. Org. Chem.*, **18**, 1233 (1953).

(11) (a) U. Schmidt and A. Mueller, *Angew. Chem.*, **75**, 299 (1963); (b) U. Schmidt, A. Mueller, and K. Markau, *Tetrahedron Letters*, **17**, 1091 (1963).

(12) E. R. Cole, *Nature*, **198**, 1083 (1963).

(13) G. Leandri and A. Tundo, *Ann. Chim.* (Rome), **44**, 63 (1954); *Chem. Abstr.*, **49**, 4563 (1955).

(14) Unpublished work of A. J. Parker and N. Kharasch, cited on p 591 of ref 2.

(15) A. Schöberl and H. Gräfje, *Ann.*, **617**, 71 (1958).

(16) S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petrol.*, **39**, 206 (1953).

(17) M. Kleiman, U. S. Patents 2,474,849 (1949) [*Chem. Abstr.*, **44**, 653 (1950)], 2,510,893 (1950) [*Chem. Abstr.*, **45**, 636 (1951)], and 2,510,894 (1950) [*Chem. Abstr.*, **45**, 637 (1951)].

(18) For discussion of related acid-catalyzed reactions, see ref 2.

TABLE III

THERMALLY INDUCED DISPROPORTIONATION OF DISULFIDES[a]

p-$XC_6H_4SS(CH_2)_2NH_3^+Cl^- \longrightarrow 0.5(p\text{-}XC_6H_4S)_2 + 0.5[S(CH_2)_2NH_3^+Cl^-]_2$

Compd	X	Disproportionation, %, after indicated no. of hr: 0.17	0.42	0.75	3	5	10	15	20	25	40	60	80	120	160	200	k, sec^{-1}[b]	$t_{1/2}$, hr
3	NO_2	51	78	95	101												1.1×10^{-3}	0.2
5	Cl						31			56	79	89					1.0×10^{-5}	19.2
4	H (68°)						11	15			36	49	57	73	81		3.2×10^{-6}	60.3
4	H (89°)						59	69	78	86							2.2×10^{-5}	8.7
6	CH_3									18				52	59	68	1.6×10^{-6}	120.3
7	CH_3O									15				47		62	1.5×10^{-6}	128.5
8	2,4,6-i-$(C_3H_7)_3$											28		47		59	1.4×10^{-6}	137.5

[a] In water and in the dark at 68°, except for the series done at 89° for calculation of ΔH_a. [b] Duplicate determinations at various time intervals with various compounds showed the reproducibility to be within 5%. In some instances, availability of limited amounts of the disulfides precluded the taking of more points for Figure 1.

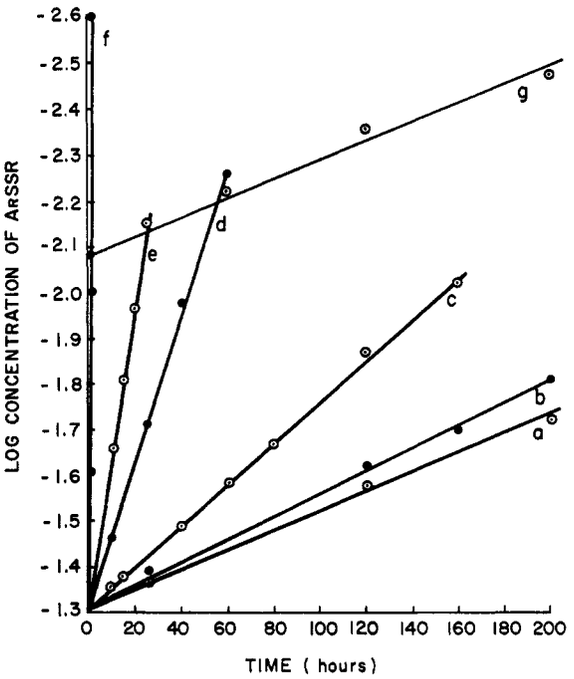


Figure 1.—First-order rate plot for the disproportionation in water of p-$XC_6H_4SS(CH_2)_2NH_3^+Cl^-$, where X is a, CH_3O (7); b, CH_3 (6); c, H (4, 68°); d, Cl (5); e, H (4, 89°); f, NO_2 (3); g, 2,4,6-i-$(C_3H_7)_3$ (8).

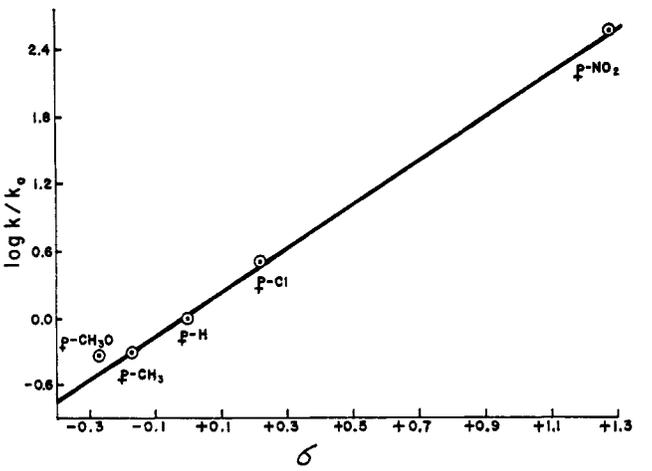


Figure 2.—Correlation of log k/k_0 at 68° with Hammett σ constants for the disproportionation of p-$XC_6H_4SS(CH_2)_2NH_3^+Cl^-$ (X as shown on plot).

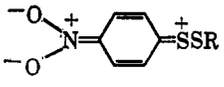
and in reaction of the free base (expt 8). Ethanol as solvent gave about the same result as water (expt 11), although the reaction was subject to a significant positive salt effect (expt 12). The reaction is accelerated both by a thiol (expt 13) and an organic base (expt 14); the organic base probably has the same effect as neutralization (expt 8) or use of alkali (expt 10).

Studies next were extended to the other disulfides of type 1 listed in Table I, under conditions first designed to maximize heterolysis and later to maximize homolysis. Kinetics of the disproportionations under heterolytic conditions were determined by isolating the sparingly soluble symmetrical aryl disulfide, which resulted when the unsymmetrical salt of type 1 was heated in water in the dark, and calculating the amount of unchanged starting material. Results in terms of "disproportionation, %" are given in Table III. Plots of the log of concentration of starting material as a function of time, shown in Figure 1 to an extent of 59–100% of completion, revealed a first-order dependence. First-order rate constants and half-lives are given in Table III. Based on reaction rates at 68 and 89° for the phenyl disulfide (4), the energy of activation was 22.6 kcal/mole. In this range of activation energy, the temperature can have a marked effect in the practical handling of unsymmetrical disulfides, as is emphasized in the half-lives for 4 of about 60 and 9 hr at 68 and 89° (Table III).

Both Table III and Figure 1 based upon it make it clear that electron-withdrawing groups greatly accelerate thermally induced disproportionation and that electron-donating groups retard it. A direct correlation of disproportionation with electronic influence from substituents in the *para* position is revealed by the linear dependence of log k/k_0 on the Hammett σ constant (Figure 2).[19] The ρ value of 1.9 is consistent with the electronic effects mentioned.

The 2,4,6-triisopropylphenyl disulfide (8) was included to gauge the possible stabilizing effect of bulky *ortho* groups, which might arise from difficulty of

(19) It is of incidental interest that the *para*-conjugated σ^- value of 1.27 was necessary for p-NO_2, rather than that of 1.04 (satisfactory for p-nitrothiophenol) [*cf.* H. H. Jaffé, *Chem. Rev.*, **53**, 222 (1953)]; justification for use of this value may be that an "alpha effect" is in operation, *i.e.*, if adjacent atoms both have free electron pairs as in the disulfide group of p-$NO_2C_6H_4SSR$, the electron donation to the ring and nitro group may be enhanced [J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962)]. To be more specific, it seems that the canonical form



is a greater contributing form than would be expected, owing to electron contribution from the second sulfur atom which adjoins the first.

formation of the hindered symmetrical aryl disulfide. The half-life of **8** is so nearly like that of the *p*-methyl compound **6**, however, that the slight difference seems only to reflect the presence of electron-donating groups having a negligible steric effect. The triisopropyl compound thus shows an interesting contrast to 2-(*t*-butyldithio)ethylamine hydrochloride, which is one of the most resistant disulfides to disproportionation we have encountered.[4] This difference in steric effects can be attributed to restricted internal rotation in *t*-butyl disulfide, which is believed to promote reactions with other disulfides to form unsymmetrical disulfides.[20] Consistent with the apparently small steric effect in the triisopropyl compound **8** is our earlier observation that 2,4,6-triisopropylphenyl disulfide shows little difference from phenyl disulfide in its ease of formation from the thiol, or in its ultraviolet absorption spectrum.[21] An earlier paper reported that *ortho* substituents affect the disproportionation of analogs of **1** considerably, even though unpredictably.[1b] A particularly puzzling feature was that the 2,6-dimethoxyphenyl compound was much less stable than the 2-methoxy.[1b] The similarity of the triisopropyl compound (**8**) and the *p*-tolyl compound (**6**) suggests that the difference in the two methoxy compounds results primarily from electronic differences, but it nevertheless seems likely that these electronic differences in turn stem from noncoplanarity of the ring and the two sulfur atoms in the 2,6-dimethoxy compound, with consequent modification of a resonance interaction which is significant for alkoxy groups but not for alkyl groups.

The order of increasing resistance toward thermal disproportionation can be summarized as $NO_2 \ll Cl < H < CH_3 \gtrsim CH_3O \gtrsim 2,4,6\text{-}(i\text{-}C_3H_7)_3$. The tolyl compound (**6**) also is included in an earlier series of approximate stabilities[4] and thus somewhat links present and earlier work.[22]

When the phenyl compound (**4**) was allowed to disproportionate in hot water containing acrylamide, no polyacrylamide could be isolated, in marked contrast to extensive polymerization during photochemically induced disproportionation (*vide infra*). This contrast suggests that thermally induced disproportionation is largely heterolytic, a conclusion confirmed by the catalytic effects of electrophiles and nucleophiles, the salt effect, and the fact that substituent effects as reflected in the σ–ρ correlation are both marked and regular[23] and are reversed under irradiation as described below.

The foregoing results help to clarify the nature of thermally induced disproportionation and of factors which influence it. Since the reaction is heterogeneous and subject to diverse influences, detailed speculation on the mechanism does not now seem appropriate. Seemingly, however, the mechanism is best understood in terms of generation of thiol or thiolate ions, which attack the unsymmetrical disulfide in a chain-type process. In strong acid, sulfenium ions (RS^+) may be important.

The role of the amino group is puzzling but probably relates to generation of thiolate ions. Earlier work,[4] and that described above, show that the free base of **1** is less stable than the salt, which in turn is less stable than the amide. The amino group therefore obviously is implicated importantly in the disproportionation; perhaps it affects pH or perhaps it assists sulfur–sulfur cleavage through an anchimeric or intermolecular interaction.

In any event, for thermally induced disproportionations, we suggest that small concentrations of thiolate ions ($XC_6H_4S^-$ and $Cl^-NH_3^+(CH_2)_2S^-$) are generated by heterolysis of the disulfide bond, possibly with anchimeric involvement of the amino group. The thiolate ions then are considered to attack the unsymmetrical disulfide (**1**), with formation of a symmetrical disulfide and a chain-propagating thiolate ion. The marked catalytic effect of mercaptoethylamine hydrochloride is thus understandable, as is the accelerating effect of alkali (which also could lead to thiolate ion). A diversity of species probably is involved in the presence of strong base or strong acid (RS^-, RS^+, RSH, and RSOH plus its disproportionation products). Nevertheless, the amount of material lost through involvement of species such as RSOH cannot be large ordinarily, at least with **4**, because we found earlier that the good material balance and products with **4** accorded well with eq 1.[1b]

Catalysis of disproportionation of disulfides by a trace of thiol is accepted as a general reaction.[25] For example, Jensen has emphasized the biological importance of disulfide redistributions based on thiol–disulfide interchange, even under very mild physiological conditions. These, he states, "appear to be chain-type reactions initiated in most cases by very small amounts of sulfhydryl compounds;" the initiating sulfhydryl group may be produced by hydrolysis of a disulfide bond.[26]

In extension of the study to disulfides **3**–**7** under conditions favoring maximum homolysis, aqueous solutions of these disulfides were simultaneously irradiated with ultraviolet light (the triisopropyl compound **8** was omitted because of its sparing solubility). Except for the phenyl compound **4**, the order of increasing resistance was inverted and became $H < CH_3 \sim CH_3O < Cl < NO_2$. The implication of a change of mechanism from the thermal process is compelling. The observed order of substituent effects is reasonable for a homolytic process: electron-donating groups should stabilize arylsulfenyl radicals ($RS\cdot$), tending to make them more like the stable RS^- species, and thus should facilitate homolytic cleavage of the disulfide bond (for example, a *p*-dimethylamino group stabilizes a benzenesulfenyl radical[11b]); conversely, electron-withdrawing groups should destabilize the radicals, tending to make them more like the highly reactive RS^+ species, and thus should disfavor cleavage. For reasons mentioned in the Experimental Section, comparison of the photochemical resistance of the *para* series with that of the *ortho* series studied earlier,[1b] seems unwise.

(20) L. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

(21) D. E. Pearson, D. Caine, and L. Field, *J. Org. Chem.*, **25**, 867 (1960).

(22) Earlier stabilities were intended as practical guides, however, and were largely done by heating in ambient light.

(23) Heterolytic processes are influenced more regularly and usually more extensively by electronic effects than are homolytic ones; *cf.*, for example, ref 24.

(24) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 693.

(25) *Cf.* E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, p 367.

(26) E. V. Jensen, *Science*, **130**, 1319 (1959).

That the photochemical mechanism is indeed mainly homolytic was substantiated by irradiating an aqueous solution of acrylamide. Polymerization occurred to the extent of 98% in the presence of the phenyl disulfide (**4**) but of only 7% in its absence. No epr signal was detectable, however, so the concentration of radicals probably is not very high.

An interrelation of heterolytic and homolytic cleavage, which probably exists under usual laboratory conditions, explains an interesting practical aspect of working with disulfides **3–8**, which was perplexing at first. With disulfides **6** and **7**, containing methyl and methoxyl groups, attempted recrystallization caused extensive disproportionation, but recrystallization was possible with **3** and **5** containing nitro and chloro groups if performed rapidly. The lower thermal stabilities of **3** and **5** therefore came as a surprise. The explanation, suggested by Cole's observation that diffuse light suffices for equilibration of disulfides,[12] is of course that **3** and **5** are the most stable photochemically even though the least stable thermally; ambient light evidently is sufficiently energetic to be troublesome with **6** and **7**. Our earlier tentative conclusion that *p*-nitro confers greater stability than *p*-CH_3 was based on stability to light, whereas other comparisons were based on thermal stability,[3] thus suggesting the need for distinguishing between stabilities under photochemical and thermal conditions.

Experimental Section[27]

Preparation of 2-(Aryldithio)ethylamine Hydrochlorides.—Preparation of 2-(*p*-methoxyphenyldithio)ethylamine hydrochloride (**7**) exemplifies the general procedure. Variations are noted in Table I. Solutions of *p*-methoxythiophenol (2.3 g, 17.0 mmoles) in 60 ml of 95% ethanol and of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (**2**, 4.36 g, 16.9 mmoles) in 30 ml of 2:1 ethanol–water were combined and stirred at room temperature for 0.5 hr. Solvent was removed and residue was taken up in 40 ml of water. Extraction with three 15-ml portions of ether removed unreacted thiol; titration with iodine of this ether extract plus the solvent distillate indicated recovery of 1.11 g (47%) of thiol. The aqueous layer was placed in contact with 20 ml of 2:1 benzene–hexane, and an ice-cold solution of 2.86 g (51.0 mmoles) of potassium hydroxide in 15 ml of water was added. The organic layer was separated and washed with 10 ml of water and then was filtered into an ice-cold solution of 2 ml of 12 *N* hydrochloric acid (24.0 mmoles) in 5 ml of water. A white precipitate formed immediately. The alkali layer was extracted twice more with benzene–hexane, and the extract was added to the acid solution as above. Precipitate was removed by filtration and amounted to 1.56 g of **7** (37% conversion, 69% yield, based on recovery of thiol), mp 149–150°. An aqueous solution of **7** was not turbid, hence *p*-methoxyphenyl disulfide was presumed absent (other disulfides also gave clear nonopalescent solutions and hence contained negligible symmetrical aryl disulfide).[1b] All of the products **3–8** had infrared absorption characteristic of aliphatic amine salts (2000–2900 cm^{-1}) and of the substituted aromatic moiety.

Influences on the Disproportionation of 2-(Phenyldithio)ethylamine Hydrochloride (4, *cf.* Table II).—Solutions of 0.222 g of **4** (1.00 mmole) in 20 ml of water or of the solvent specified in Table II (all solutions were 0.05 *M* in **4**) were heated at 68 ±0.01° for 3, 10, and 15 hr. The flask then was withdrawn and was chilled in ice. Contents of the reaction flasks were extracted with three 15-ml portions of ether. The combined ether layers were washed with 10 ml of water and dried. The ether was removed and the samples were dried to constant weight under reduced pressure. Phenyl disulfide formed was characterized by its infrared spectrum and/or its melting point. Occasionally cystamine dihydrochloride also was isolated from the aqueous layer and characterized as a check. In certain of the experiments, obvious necessary changes in isolation were made; for example, in expt 11 ethanol was removed and the products were mixed with water before ether extraction, and in expt 8, 10, and 14 the amines were extracted from the ether before it was evaporated.

All disproportionations reported in Table II were carried out in flasks shielded to the neck in a constant-temperature bath containing dark oil, except for expt 3 and 4. In expt 1 and 5–14, additional shielding was supplied by wrapping the flasks with aluminum foil. The light-induced reactions (expt 3 and 4) were performed by suspending the flasks in refluxing methanol–ethanol (2.4:1, temperature 68°). "Oxygenation" was done by passing oxygen over the surface of the solution for several minutes, and "degassing" by passing nitrogen into the flask three times and twice evacuating. "Disproportionation, %" was calculated as (mmoles of phenyl disulfide formed × 2 × 100)/(1 mmole of **4** used).[3]

Influence of *para* Substituents on the Disproportionation of 2-(Aryldithio)ethylamine Hydrochlorides. A.—Thermally Induced Disproportionation.—Experimental conditions and isolations of the symmetrical aryl disulfides were the same as in the study of influences on the disproportionation of **4**. The temperature was 68°, flasks were wrapped in foil, and solutions contained 1.00 mmole of disulfide in 20 ml of water (0.05 *M*). Symmetrical aryl disulfides were characterized by their infrared spectrum and/or melting point. In the disproportionation of 2-(*p*-nitrophenyldithio)ethylamine hydrochloride (**3**) the insoluble *p*-nitrophenyl disulfide was isolated by filtration (*p*-nitrophenyl disulfide is insoluble in ether and only sparingly soluble in other organic solvents).

In the disproportionation of 2-(2,4,6-triisopropylphenyldithio)-ethylamine hydrochloride (**8**), owing to its limited solubility in water, 0.174 g (0.5 mmole) was partly dissolved and partly suspended (68°) in 60 ml of water (0.0083 *M*); three 25-ml portions of ether were used for extraction. Since not quite all of the **8** dissolved at zero time, the validity of the rate constant and therefore of the half-life for this disproportionation may be somewhat questionable; however, all of **8** had dissolved at least by the time the first point was taken (60 hr).

"Disproportionation, %" for Table III was calculated as for Table II. Rate constants (Table III) were obtained by plotting the log of the concentration of unreacted unsymmetrical disulfide against time (Figure 1), unreacted disulfide being calculated from aryl disulfide isolated. The slope of these plots was multiplied by 2.303 to obtain the rate constants. As a further check, concentrations of unreacted unsymmetrical disulfide at various times were inserted in the equation $k = (2.303 \log C_0/C)/t$. Half-lives (Table III) were calculated from the equation $t_{1/2} = 0.693/k$. For the energy of activation in the disproportionation of **4**, the reaction was repeated at 89° and calculations from *k* at 68 and 89° were done using the equation $\log k_2/k_1 = \Delta H_a(T_2 - T_1)/2.303RT_2T_1$.

B. Photochemically Induced Disproportionation.—Aqueous solutions of 0.5 mmole of unsymmetrical disulfide in 30 ml of water (0.0167 *M*) in 125-ml Pyrex erlenmeyer flasks were all irradiated simultaneously through the bottoms of the flasks at a distance of 5 in. (ultraviolet source as in Table II, footnote *a*). Flasks were suspended in a circle above the lamp to give a common geometry, and irradiation was for 25 min at room temperature (heat from the lamp increased the temperature to *ca.* 35° at the surface of the flasks). The concentrations specified were used because 0.0167 *M* represents a nearly saturated solution for the sparingly soluble nitro compound (**3**). Values of "disproportionation, %," calculated as usual for *p*-$XC_6H_4SS(CH_2)_2NH_3^+Cl^-$ containing various X groups, were NO_2 (**3**), 38; Cl (**5**), 67; CH_3O (**7**), 73; CH_3 (**6**), 74; H (**4**), 100.[28]

Experiments on the Nature of the Disproportionation. A.—Acrylamide (9 g) and the phenyl disulfide **4** (0.222 g) were dissolved in 20 ml of water in a shielded flask and the mixture was heated at 68° for 80 hr (*ca.* 60% disproportionation would be anticipated from earlier results). No polyacrylamide was

(27) Melting points are corrected. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained with neat liquids or Nujol mulls using a Perkin-Elmer Model 137B spectrophotometer.

(28) In a comparison of *ortho* substituents, **4** was 53–95% disproportionated,[1b] depending on the geometry of samples relative to the source. Since the concentration then was 0.05 *M* and since we have found it difficult to reproduce photochemical experiments done at different times, comparison of the present *para* values with the *ortho* values[1b] would be unwise.

visible. Dilution with acetone (170 ml), in which acrylamide but not polyacrylamide is soluble,[29] gave a small amount of fluff, but cooling and filtration resulted only in 0.125 g (maximum polymerization, *ca.* 1%).

B.—Acrylamide (9.0 g) and the disulfide **4** (0.222 g) in 20 ml of water were irradiated as usual for 1 hr. The solution became viscous and rubbery solid formed on the flask wall. Liquid was decanted, and the mass of solid was dried under vacuum (18 hr) to yield a hard solid weighing 8.82 g (98% polymerization).

Repetition of the experiment without **4** resulted in no signs of polymerization. Dilution with 170 ml of acetone resulted in opalescence, and chilling gave only 0.6 g of fluff (maximum polymerization, *ca.* 7%).

(29) J. R. Cox, Jr., C. L. Gladys, L. Field, and D. E. Pearson, *J. Org. Chem.*, **25**, 1083 (1960).

C.—A 0.5 *M* solution of disulfide **4** (0.222 g in 2 ml of water) in a 0.1-cm cell was irradiated at room temperature from a distance of 5 cm with the usual source. No epr signal developed at 9.5 kMc using a V 4548 aqueous solution sample cell in a V 4531 multipurpose cavity. The instrument was equivalent to a Varian 4502-00 audiomodulated epr spectrometer. The range was 2.9–3.5 kgauss.[30]

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(30) We are indebted for this measurement to Professor Walter Bouldin and Mr. Robert Hankla of the Department of Physics at Vanderbilt University.

Organic Disulfides and Related Substances. XIX. Alkyl and Aryl Dithiosulfites[1a,b]

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Typical symmetrical and unsymmetrical dithiosulfite esters, RSS(O)SR′, were prepared. Two moles of *t*-butyl dithiosulfite decompose cleanly when heated to give 1 mole each of *t*-butyl disulfide, *t*-butyl trisulfide, and sulfur dioxide; this decomposition seems general for dithiosulfites. Most of the dithiosulfites studied proved to be quite unstable, the relative stability usually decreasing in the order *t*-alkyl ≫ aryl > *sec*-alkyl ≫ primary alkyl (usually not isolable). Decomposition follows first-order kinetics, is strongly catalyzed by sulfur dioxide, and involves scrambling of groups. In their reactions with a thiol, an enolate, and alkali, dithiosulfites resemble thiolsulfonate and thiolsulfinate esters, RSO_2SR and RS(O)SR.

Several authors have reported dithiosulfites, $(RS)_2SO$, but with little or no characterization.[2] Dithiosulfites also have been postulated as intermediates in the decomposition of amidothiosulfites, RNHS(O)SR.[3] Only recently, however, have two reasonably stable dithiosulfites been isolated and characterized, *t*-butyl dithiosulfite (**1**)[4a,b] and dicyano-1,2,3-trithiole-2-oxide(**2**).[4c-e]

Our early efforts to synthesize dithiosulfites were hampered by facile decomposition which seemed characteristic of the class. As a prelude to further synthetic work, therefore, the nature of the decomposition was examined with *t*-butyl dithiosulfite (**1**) as a model. If the decomposition were understood, there was good prospect of assessing relative stabilities of dithiosulfites and consequently of choosing those most likely to be stable enough to warrant preparative effort.

In preparing the model (**1**), which ultimately was obtained in a purer state than heretofore,[4a] modification of the method of Wolff proved the most satisfactory of a number of approaches tried.[4] This modification involved addition of the thiol and pyridine to an equivalent quantity of thionyl chloride, as shown by eq 1.

$$2RSH + SOCl_2 \xrightarrow{C_5H_5N} RSS(O)SR \qquad (1)$$

Ether was used as a solvent because of its adaptability with structures of interest, but hydrocarbons may be better when they can be used.[4] The inverse procedure, in which thionyl chloride is added to the thiol and pyridine, probably would favor formation of disulfide by thioalkylation (*vide infra*). Use of the sodium salt of the thiol with thionyl chloride (in the absence of pyridine) afforded no dithiosulfite.

Although the ester **1** is quite stable at 100°, at 185° total decomposition ensued in less than 1 hr. Analysis of the products revealed that the reaction is that of eq 2.

$$2(RS)_2SO \longrightarrow RSSR + RSSSR + SO_2 \qquad (2)$$

The weight of the mixture of sulfides was 96% of that required by eq 2, and the ratio of *t*-butyl disulfide to trisulfide was 1 ± 0.1 by gas–liquid partition chromatographic (glpc) analysis. Sulfur dioxide amounted to 96% of 1 mole for each 2 of dithiosulfite. Heating of **1** at 200° in a glpc column showed that total peak area comprised 5% **1**, 42% disulfide, and 48% trisulfide; at other temperatures, the essentially 1:1 ratio of di- to trisulfide persisted. Studies of the thermal decomposition of isopropyl, *n*-butyl, and phenyl dithiosulfite suggest the generality of eq 2.

The products of eq 2 suggested a method for comparing the stabilities of dithiosulfites without extensive purification. Syntheses were accomplished as usual, and the crude reaction mixtures were washed free of as many contaminants as possible. Ether was removed and the residues then were heated at 100°. The time required for the characteristic strong infrared absorption of the SO moiety (at 1110–1145 cm^{-1}) to diminish to one-half of its original value was determined. This half-life, although approximate, furnished an index of

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract DA-49-193-MD-2030. Abstracted from part of the Ph.D. dissertation of W. B. L., Vanderbilt University, Aug 1965; (b) Paper XVIII: L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966); (c) National Defense Education Act Fellow, 1961–1964.

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