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Ultraviolet Spectra of Alkyl Disulfides and their Relation to Alkali Cleavage of Disulfide Bonds[1,2]

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Successive alkylation of the α-carbon atom in dimethyl disulfide is accompanied by a hypsochromic shift in the ultraviolet absorption maximum. For every substitution of a hydrogen atom on the α-carbon there is a displacement of 2.5 mμ. Loss of the characteristic absorption maximum in the region of 250 mμ is attributed to loss of the ability to donate an electron pair to sulfur. The acidity of the C–H bond situated alpha to the S–S linkage is the basis for a proposed new mechanism for the alkali cleavage of alkyl disulfides. Here base attack is believed to occur at an activated α-C–H bond resulting in carbanion formation; the latter subsequently effects S–S bond rupture *via* a modified β-elimination process in which both a thiol and a thiocarbonyl compound are produced. In the case of dithiodiacetic acid the products formed on alkali decomposition are demonstrated to be thioglycolic and thioglyoxylic acids, the C=S group of the latter being characterized by an absorption maximum at 335 mμ.

Introduction

In an earlier paper[4] it was suggested that a correlation exists between the structure of alkyl disulfides and their susceptibility to alkali cleavage. In particular, it was argued that the changes of the ultraviolet spectra with *p*H of many of these substances was a measure of the acidic character of the hydrogen atoms in the α-position to the disulfide linkage. A mechanism for the alkali cleavage of alkyl disulfides was proposed involving a base attack on these hydrogens.

It is the purpose of the present paper to introduce evidence in support of our mechanism and to evaluate previously proposed mechanisms of alkali attack of the disulfide bond. The mechanism is applied to a number of systems in order to evaluate its scope.

Experimental

The ultraviolet spectra were determined with a calibrated Beckman DU spectrophotometer and matched quartz cells of 1-cm. path length using Eastman Kodak Co. spectral grade solvents. The majority of the simple alkyl disulfides and thiols utilized in this study were Eastman Kodak Co. white label grade chemicals which were subjected to repeated fractional distillation prior to spectral examination.

The diisopropyl disulfide, prepared by oxidation of the corresponding thiol with hydrogen peroxide employing the procedure reported by McAllan, Cullum, Dean and Fidler,[5] had b.p. 58° (11 mm.), n^{25}D 1.4892. They report values b.p. 174° (760 mm.), n^{25}D 1.4891.

The three isomeric unsymmetrical methyl butyl disulfides, *viz.*, methyl *n*-butyl, methyl *sec*-butyl and methyl *t*-butyl disulfides, were prepared following the disproportionation technique of Birch, Cullum and Dean,[6] by treating the appropriate butyl thiol isomer with dimethyl disulfide in the presence of an alkali catalyst. By means of repeated fractionations, it was possible to isolate these unsymmetrical disulfides chromatographically pure, as determined by gas chromatography in Burrell model K-5, employing a 2-meter apiezon L column maintained at 150°.

Methyl *n*-butyl disulfide had b.p. 45° (4 mm.), n^{25}D 1.5005. *Anal.* Calcd. for $C_5H_{12}S_2$: C, 44.12; H, 8.82; S, 47.06. Found: C, 43.90; H, 9.04; S, 46.96.

Methyl *sec*-butyl disulfide had b.p. 21° (1 mm.), n^{25}D 1.5008. *Anal.* Calcd. for $C_5H_{12}S_2$: C, 44.12; H, 8.82; S, 47.06. Found: C, 44.81; H, 8.73; S, 46.84.

Methyl *t*-butyl disulfide had b.p. 79° (68 mm.), n^{25}D 1.4947. The reported values[6] are b.p. 69° (42 mm.), n^{20}D 1.4975. *Anal.* Calcd. for $C_5H_{12}S_2$: C, 44.12; H, 8.82; S, 47.06. Found: C, 44.89; H, 8.89; S, 47.00.

The above analyses were performed by the Schwarzkopf Laboratories, Woodside, L. I., N. Y.

4,4′-Dithiodimorpholine, obtained from Eastman Kodak Co., was purified by several recrystallizations from a hot aqueous solution of dimethylformamide. The observed m.p. 124–125° agrees with the value reported by Blake.[7]

D-Penicillamine disulfide was prepared in the manner described by Berg and Folkers[8] by catalytic air oxidation of D-penicillamine (obtained as a gift through the generosity of Professor V. du Vigneaud of the Cornell Medical School). A sample twice recrystallized from aqueous acetone solutions melted at 199–200°.

2,2′-Dithiobisethylamine hydrochloride was prepared in an analogous manner by the air oxidation of 2-mercaptoethylamine (Evans Chemetics) to the corresponding disulfide, which in turn was converted to the hydrochloride by passing dry hydrogen chloride through an anhydrous methanol solution containing this material. The crystalline material so obtained was washed with methanol, then ether, followed by vacuum drying over sodium hydroxide pellets. The product had m.p. 215–216.5°.

Dithiodiacetic acid, m.p. 107°, was prepared similarly by the air oxidation of thioglycolic acid (Eastman Kodak Co.) in the presence of iron(III) catalyst according to the method of Biilmann.[9]

β,β'-Dithiodipropionic acid was prepared from β-mercaptopropionic acid (Sharples) by simple aqueous oxidation of a solution of this acid employing 0.1 *N* iodine solution. The appearance of iodine color served to indicate the end of the reaction. The resulting disulfide was extracted with ether. After drying and removal of the ether on a steam-bath, the product was recrystallized twice from a benzene–petroleum ether mixture and was found to melt at 156–157° in agreement with the literature value obtained by Biilmann.[10]

γ,γ'-Dithiodibutyric acid, m.p. 107°, was prepared by treating butyrolactone (Eastman Kodak Co.) with sodium disulfide in 1-butanol according to the method of Reppe.[11]

l-Cystine, obtained from Schwarz Laboratories, had $[\alpha]$D-208° in 1 *N* hydrochloric acid.

Glyoxylic acid was specially prepared as a 95% solution in water by Kay–Fries Chemicals, Inc., New York, N. Y. *via* the hydrolysis of methyl dimethoxyacetate.

Dichloroacetic acid, also obtained by Kay–Fries, was freshly distilled prior to use.

Thioglyoxylic acid was prepared in solution by two techniques. In one, equimolar solutions of glyoxylic acid and Na_2S dissolved in deoxygenated water were mixed in a stoppered volumetric flask, from which air had been purged by a nitrogen flushing, and allowed to stand at 30° for a period of 6 hours before its spectra were taken.

In a comparable manner a solution of (2.5×10^{-1} *M*) dichloroacetic acid, was mixed with an equimolar concentration of $Na_2S \cdot 9H_2O$ dissolved in 0.25 *N* NaOH and allowed

(1) Presented at the 126th National Meeting of the American Chemical Society, New York City, September, 1954.

(2) Taken in part from the Ph.D. thesis of Norman A. Rosenthal, Polytechnic Institute of Brooklyn, June, 1955.

(3) Research Fellow 1952–1954, National Heart Institute, U. S. Public Health Service.

(4) N. A. Rosenthal and G. Oster, *J. Cosmetic Chemists*, **5**, 286 (1954).

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

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

(7) E. S. Blake, *J. Am. Chem. Soc.*, **65**, 1267 (1943).

(8) C. Berg and K. Folkers, British Patent 621,915, April 7, 1949.

(9) E. Biilmann, *Ann.*, **348**, 131 (1905).

(10) E. Biilmann, *ibid.*, **339**, 366 (1905).

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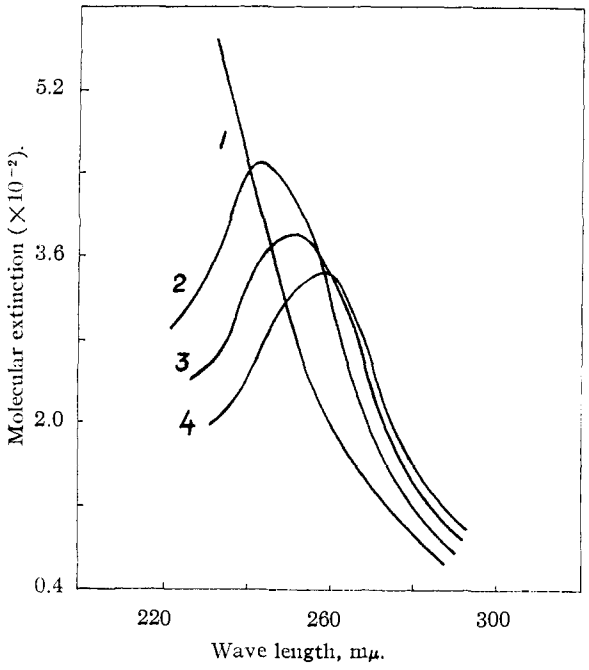


Fig. 1.—Spectra of α-substituted disulfides in methanol: 1, di-*t*-butyl disulfide; 2, diisopropylyl disulfide; 3, dipropyl disulfide; 4, dimethyl disulfide.

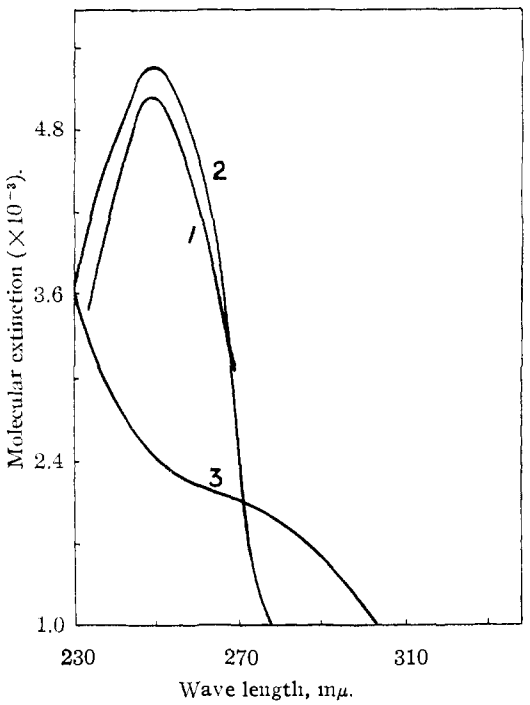


Fig. 2.—Effect of hydrogen ion on the ultraviolet spectrum of 4,4′-dithiomorpholine: 1, methanol; 2, 0.1 *N* sodium methoxide in methanol; 3, methanol containing 4.5 × 10^{-4} mole/l. of acetic acid.

to stand at 25°. The ultraviolet absorption of the resulting yellow solution was recorded on dilution after 20 hours.

Results and Discussion

The ultraviolet spectra of increasingly substituted alkyl disulfides are illustrated in Fig. 1, and their maxima are listed in Table I. Examination of the data in this table reveals that successive symmetrical replacement of a pair of hydrogen atoms by methyl groups is accompanied by a shift of about 5 mμ toward shorter wave lengths. There is also an accompanying increase in the molecular extinction coefficient. Complete substitution, as with *t*-butyl disulfide, results in transparency in this wave length region.

This same hypsochromic shift, namely, 2.5 mμ per replaced α-hydrogen, is demonstrated for unsymmetrically substituted disulfides; for example, the isomeric methyl butyl disulfides, methyl *n*-butyl, methyl *sec*-butyl and methyl *t*-butyl disulfides.

An indication that the origin of these ultraviolet spectral shifts does not arise from steric repulsive interactions of α-alkyl substituents leading to distortion of the S–S bond orbitals is evident in the work of Bergson.[12] In the case of alkyl diselenides, similar hypsochromic displacements of the ultraviolet maxima also have been observed to accompany the replacement of α-hydrogens by alkyl substituents, despite the fact that the larger covalent radius of Se (1.17 Å.) as compared to S (1.04 Å.) would be expected in the diselenides to reduce greatly the possibility of steric repulsion resulting from α-alkyl substituent interactions.

The hyposochromic shift of the spectra of substituted disulfides occurring in the sequence methyl > ethyl > isopropyl > *t*-butyl is characteristic of hyperconjugation. Baker[13,14] observed for a series of alkyl substituted benzenes that displacement of the absorption maximum to shorter wave lengths was dependent in the number of available hydrogens.

In an entirely analogous manner we believe that the observed relationship between the number of available α-hydrogen atoms present in an alkyl disulfide and its corresponding ultraviolet spectrum could result from the interaction of the electrons on the α-carbon atom with 3d-orbitals of the sulfur resulting in octet expansion (b).

$$-CH_2-S-]_2 \longleftrightarrow H^+ \; -C\overline{H}-S-]_2 \longleftrightarrow -CH=S-]_2$$
$$\text{(a)} \qquad\qquad \text{(b)}$$

Further evidence tending to confirm this interpretation of the origin of the ultraviolet disulfide spectra is evident in the spectral transformations observed in 4,4′-dithiodimorpholine (Fig. 2) in which the S–S bond is linked directly to nitrogen rather than carbon. Here the necessary electron pair required by sulfur for octet expansion is available in the form of the unshared electron pair on nitrogen. The addition of a hydrogen ion, with resulting ammonium salt formation, could immobilize the unshared electron pair on nitrogen, rendering it unavailable for donation to sulfur. The consequence of such action would result in the disappearance of the characteristic 250 mμ absorption maximum. This effect is realized when either a small quantity of acetic acid sufficient for salt formation is added to the solution of 4,4′-dithiodimorpholine (Fig. 2) or the effect is reversed on

(12) G. Bergson, *Arkiv. Kemi*, **9**, 121 (1956).

(13) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1844 (1935).

(14) J. W. Baker, "Hyperconjugation," Oxford University Press, London, 1952.

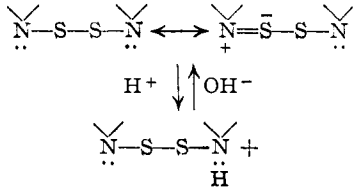
TABLE I

ULTRAVIOLET ABSORPTION OF DIALKYL DISULFIDES

Disulfide	λmax, mμ	ε max	Solvent	Ref.
CH_3SSCH_3	253	170	Vapor	a
	254.5	340	EtOH	a
	255	361	Hexane	b
	256	343	MeOH	
	254	320	Cyclohexane	c
$CH_3SS(CH_2)_3CH_3$	252	356	MeOH	
$CH_3CH_2SSCH_2CH_3$	251.5	420	EtOH	d
	250	430	Hexane	b
	250	440	Cyclohexane	c
$CH_3SSCH(CH_3)(C_2H_5)$	250	417	MeOH	
$CH_3SSC(CH_3)_3$	248	483	MeOH	
$(CH_3)_2CHSSCH(CH_3)_2$	244	445	MeOH	
$(CH_2)_5CHSSCH(CH_2)_5$	246	560	EtOH	e
$(CH_3)_3CSSC(CH_3)_3$	Opt. transparent		MeOH	
$[HCl\cdot NH_2CH_2CH_2-S]_2$	246	386	Water	
$HOOCCH_2SSCH_2COOH$	Opt. transparent		Water	
$HOOC(CH_2)_2SS(CH_2)_2COOH$	(243)	275	0.1 *N* HCl	
	243	542	Water	
	248	630	0.01 *N* NaOH	
$HOOC(CH_2)_3SS(CH_2)_3COOH$	248	542	MeOH	
	248	542	0.02 *N* NaOMe in MeOH	

[a] G. R. Brandt, H. J. Emeleus and R. W. Haszeldine, *J. Chem. Soc.*, 2190 (1952). [b] G. Gorin and G. Dougherty, *J. Org. Chem.*, 21, 24 (1956). [c] W. E. Haines, R. V. Helm, and J. S. Ball, *J. Phys. Chem.*, **58**, 274 (1958). [d] H. Ley and B. Arends, *Z. physik. Chem.*, B15, 311 (1932). [e] H. P. Koch, *J. Chem. Soc.*, 387 (1949).

rendering the solution alkaline. These transformations are represented by



In summary, the chromophore responsible for aliphatic disulfide absorption appears to be of the general form $-\ddot{X}-S- \longleftrightarrow X=\bar{S}-$ where X can be nitrogen or carbon. The requisite electron pair capable of being donated to the sulfur for octet expansion arises from either α-hydrogen hyperconjugation or from the unshared electron pair on nitrogen. There are a number of disulfides, such as dibenzyl disulfide, allyl disulfide and dithiodiglycolic acid, which, owing to competitive resonance interactions, are incapable of donating electron pairs to sulfur. These disulfides are optically transparent (Fig. 3). Thus for allyl disulfide, resonance interaction occurs as[15]

$$CH_2=CH-\bar{C}H-S-]_2 \longleftrightarrow CH_2-\bar{C}H=CH-S]_2$$

Dithiodiglycolic acid and its homologs β,β′-dithiodipropionic and γ,γ′-dithiodibutyric acids all exhibit different spectral characteristics. Dithiodiglycolic acid is optically transparent up to a *p*H value of about 12 above which the solution becomes bright yellow with an ultraviolet maximum at 335 mμ (Fig. 4) which increases with time indicative of a kinetic process. The propionic homolog is sensitive to *p*H changes and exhibits two distinct spectral forms. In strong acid (0.1 *N* HCl) it is essentially transparent while in base it has an absorption maximum at 248 mμ. The next higher homolog γ,γ′-dithiodibutyric acid with a maximum at 250 mμ is independent of *p*H changes.

Alkyl disulfides (with the sole exception of *t*-alkyl disulfides) can be arranged into two groups ac-

(15) D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.*, **74**, 48 (1952).

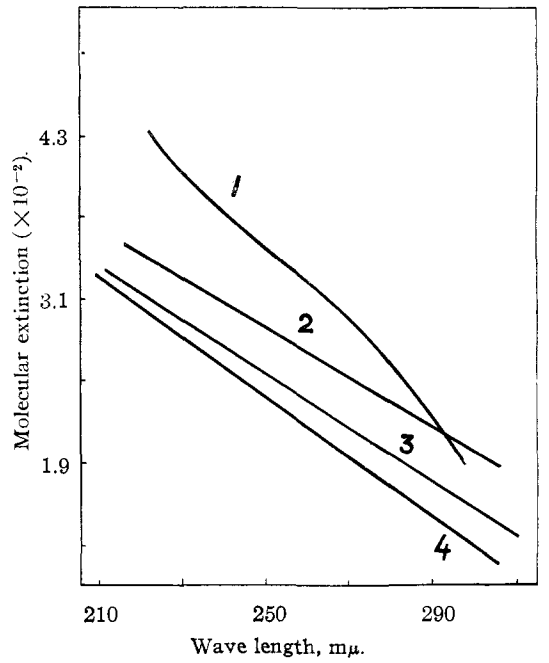


Fig. 3.—Optically transparent alkyl disulfides: 1, dibenzyl disulfide in methanol; 2, allyl disulfide in ethanol; 3, penicillamine disulfide in 0.1 *N* NaOH; 4, penicillamine disulfide in 0.1 *N* HCl.

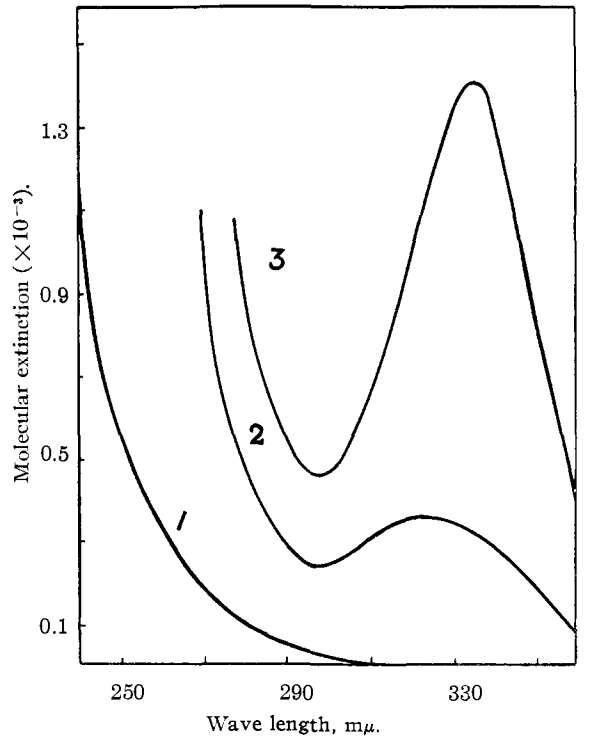
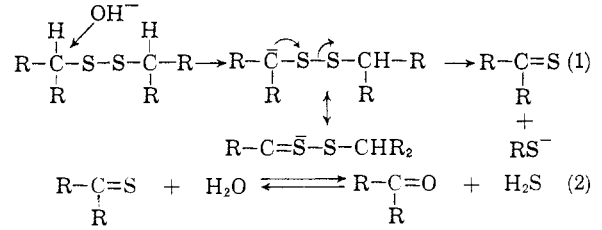


Fig. 4.—Spectrum of dithiodiglycolic acid: 1, in H_2O; 2, in 0.02 *N* NaOH initially; 3, in 0.02 *N* NaOH 72 hours later.

cording to their spectral characteristics. In the first group are those compounds which are either optically transparent or are *p*H dependent. In the second group are those disulfides absorbing in the region of 250 mμ and whose spectra are insensitive to changes in *p*H. A characteristic of the compounds of the first group is the acidic nature of their α-hydrogens. The greater the degree of acidity of the α-hydrogen the greater is the difference in spectral character from that of the *p*H insensitive disulfides. Coincident with enhanced α-hydrogen acidity is the alkali lability of these disulfides. Thus, whereas dimethyl disulfide requires heating with alkali in a sealed tube at 150° for a period of 5 hr. to effect disulfide cleavage,[16] cystine[17] and β,β′-dithiopropionic acid[18] will decompose in base under much less drastic conditions. Far greater alkali lability is exhibited by dibenzyl disulfide[19] and by α,α′-dithiodiacetic acid[20] which decompose rapidly at room temperature.

Schöberl and co-workers[21] studied the alkali decomposition of a series of α,α′-dithiodicarboxylic acids and found that the decomposition products of these disulfides could all be accounted for in terms of three types of reaction products, namely, H_2S, a thiol and either an aldehyde or ketone. Schöberl postulated the direct hydrolytic cleavage of the disulfide bond resulting in the formation of a thiol and sulfenic acid, the latter further decomposing to yield H_2S and the corresponding carbonyl compound. This mechanism postulates sulfenic acid intermediates, the existence of which is doubtful, and it does not allow for the prediction of the relative alkali lability of different alkyl disulfides.[4,22] On the basis of our evidence of the acidic nature of the α-C–H bond it would appear that this would be the more probable site of base attack. As a consequence, alkali cleavage would arise according to the scheme



The carbanion formed in the primary step may be stabilized by expansion of the sulfur octet and may subsequently *via* a concerted process effect the cleavage of the S–S bond by means of a β-elimination type reaction. The primary alkaline decomposition products would be a thiol and a thiocarbonyl compound. The existence of reaction 2 is believed to account for the presence of H_2S almost invariably observed to occur. The previously observed alkali decomposition products[23] of dithiodiglycolic acid, namely, glyoxylic, thioglycolic and oxalic acids, as well as H_2S do not account for the observed absorption maximum at 335 mμ shown in Fig. 4, inasmuch as none absorb in this spectral region. According to our scheme, the compound absorbing at 335 mμ should be the thioaldehyde, thioglyoxylic acid.

Thioglyoxylic acid in the form of its sodium salt was prepared in solution[24] by dissolving equimolar quantities of sodium sulfide and sodium dichloroacetate in water. The resulting solution after a short period of time turned an intense yellow color exhibiting a sharply defined absorption maximum at 335 mμ. The assignment of the 335 mμ absorption maximum to thioglyoxylic acid clearly establishes the identity of the unknown chromophore formed during the alkaline decomposition of dithiodiglycolic acid. In the second method, equimolar quantities of Na_2S and glyoxylic acid were mixed, whereupon a yellow colored solution developed which also displayed an absorption maximum at 335 mμ.[25] This result clearly indicates that in the presence of water as a solvent an equilibrium between thioglyoxylic acid and glyoxylic acid and H_2S is established.

A counterpart of the mechanism proposed here for the alkali cleavage of alkyl disulfides has been reported by Kornblum[26] to occur in the base cleavage of alkyl peroxides. In this instance, the O–O bond replaces the disulfide linkage, with alcohol being formed in place of thiol and carbonyl in place of thiocarbonyl.

Re-examination of the literature reveals that evidence for the formation of thiocarbonyls during the alkaline decomposition of dithiodiglycolic acid has long been existent. In their studies of the action of sodium hydroxide upon a series of diaryl diamides of dithiodiglycolic acid, Frerichs and Wildt[27] invariably isolated thioglycolic acid, H_2S and a thiocarbonyl-containing compound. In the case of dithiodiglycolyldianilide, they demonstrated that the yellow thioöxanilide formed in the reaction had the assigned structure by independent synthesis as well as by quantitative oxidation to oxanilide. These workers also noted that the alkali decomposition of the selenium counterpart diselenobisacetanilide yielded the selenium analogs, namely, selenoglycolic acid and selenoöxanilide. It would therefore appear that our mechanism for the base-catalyzed decomposition of disulfides is of a general nature and applies equally well both to alkyl peroxides and to diselenides.

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(19) T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **97**, 1175 (1910).
(20) W. Stricks and I. M. Kolthoff, *J. Am. Chem. Soc.*, **73**, 4569 (1951).
(21) A. Schöberl, E. Berninger and F. Harren, *Ber.*, **67B**, 1545 (1934); A. Schöberl and M. Wiesner, *Ann.*, **507**, 111 (1933).
(22) F. Asinger, M. Thiel and W. Schaefer, *ibid.*, **637**, 148 (1960).
(23) A. Schöberl and P. Rambacher, *ibid.*, **538**, 84 (1939).
(24) M. H. Brunel, *Bull. soc. chim. France*, **15**, 134 (1896).
(25) The chromophore in thioglyoxylic acid responsible for the 335 mμ absorption maximum is of the form —C(=S)—C(=O)—. Campaigne (E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956)) has indicated that α-thiopyruvic acids, which possess the same basic structural features, are yellow and absorb in the neighborhood of 330 mμ.
(26) N. Kornblum and H. E. DeLaMare, *J. Am. Chem. Soc.*, **73**, 880 (1951).
(27) G. Frerichs and E. Wildt, *Ann.*, **360**, 105 (1908).