

carbamyl Chloride.—The mercaptide was prepared by addition of 2.44 g. (0.02 mole) of methyl mercaptoacetate to 0.460 g. (0.02 g.-atom) of sodium in 4 ml. of absolute methanol. The solution was added to 100 ml. of anhydrous ether and the solid washed by decantation with ether. The mercaptide IV was suspended in 60 ml. of acetonitrile and added to a solution containing 2.32 g. (0.02 mole) of *t*-butyl thiocyanate (X, present as 3.17 g. of an oil containing 73.3% thiocyanate and 26.7% isothiocyanate) and 4.63 g. (0.02 mole) of N,N-diphenylcarbamyl chloride in 200 ml. of acetonitrile. The reaction mixture was stirred 10 hr. at 45–50° under nitrogen.

Isolation of the products in the manner previously described afforded 4.92 g. (82%) of the N,N-diphenylthiocarbamate derivative of methyl mercaptoacetate (VI), m.p. 113–114°. Analysis of the liquid portion in the vapor fractometer indicated 1.98 g. (85.5%) of *t*-butyl thiocyanate (X); 0.8 g. (94%) of *t*-butyl isothiocyanate was recovered unchanged. No other peaks were noted using either the thiocyanate or methyl 5,5-dimethyl-3,4-dithiahexanoate calibration conditions.

General Conditions for Cyanide Cleavage and Recombination Reactions.—The cyanide cleavage and recombination reactions were carried out in purified acetonitrile using the conditions previously described.⁵ Sodium isopropyl mercaptide (XIX) and sodium isobutyl mercaptide (XX) were prepared by the method previously described for sodium carbomethoxymethyl mercaptide (IV).⁵ In reactions involving DPCC a single equivalent was used. Analysis of the reaction mixtures were performed using either an F and M Model 500 vapor fractometer with a Honey-

well recorder or a Perkin-Elmer Model 154C vapor fractometer with a Brown recorder. Glass columns (4 mm., 22 in.) were packed with 4.0% Carbowax 400 on Chromosorb P (60/80 mesh) or in some cases 30/60 mesh. Yields of the volatile products were obtained from standard calibration curves of each pure component. Ethyl benzoate and toluene were used as internal standards. The calibration conditions and retention times of the various components are shown in Table II. The nonvolatile reaction products were isolated by crystallization and compared with authentic samples.

Formation of Dimethyl 3-Thiaglutarate (XVIII) from III and IV.—A suspension of 0.640 g. (0.005 mole) of freshly prepared mercaptide IV in 25 ml. of acetonitrile was treated with 0.656 g. (0.005 mole) of III. The suspension was stirred under a nitrogen atmosphere for 12 hr. at 50°. The brown solid (0.250 g.) was filtered and the acetonitrile removed *in vacuo*. Analysis of the remaining oil (0.766 g.) in the vapor fractometer indicated the presence of 77.8% of XVIII. An infrared spectrum of the oil was identical with that of an authentic sample.¹¹

Reaction of Methyl 5-Methyl-3,4-dithiahexanoate (XVI) with Sodium Carbomethoxymethyl Mercaptide (IV).—A solution containing 0.450 g. (0.0025 mole) of XVI in 75 ml. of acetonitrile was treated with a suspension of 0.320 g. (0.0025 mole) of IV in 75 ml. of acetonitrile. After 12 hr. at 50° the vapor fractogram of the reaction mixture showed the presence of 28.4% XVI, 2.0% XVIII, as well as considerable amounts of dimethyl 3,4-dithiaadapate (XXI). The symmetrical disulfide XXI was identified by comparison of the retention time with that of an authentic sample.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C.]

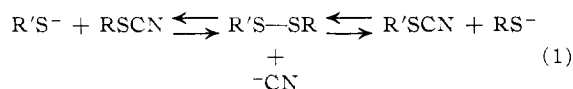
Chemistry of Aliphatic Disulfides: VII. Cyanide Cleavage in the Presence of Thiocyanates^{1,2}

BY RICHARD G. HISKEY AND DAVID N. HARPP

RECEIVED SEPTEMBER 25, 1963

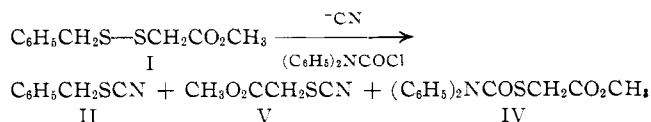
Cleavage of several unsymmetrical disulfides containing a *t*-butyl group was conducted in the presence of phenyl or benzyl thiocyanate. In the examples studied cyanide ion was found to attack the more positively polarized sulfur atom and displace *t*-butyl mercaptide. The mercaptide was scavenged by the added thiocyanate and was obtained as a new unsymmetrical disulfide.

In the preceding paper² the equilibria established during cleavage of an unsymmetrical disulfide with cyanide ion was shown to involve the primary cleavage products and the unsymmetrical disulfide (eq. 1) rather than another type of adduct formed by recombination of the primary cleavage products.

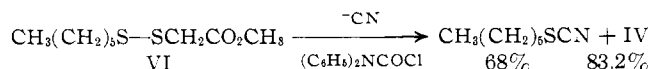


Earlier experiments on the cleavage of unsymmetrical aryl alkyl³ and dialkyl⁴ disulfides in the presence of a mercaptide scavenger suggested that cyanide cleavage gave the more stable mercaptide (the mercaptan of lower pK_a) and the corresponding thiocyanate as the predominant products. The extent of selective attack appeared to depend on the relative anionic stability of the two mercaptans comprising the disulfide. For example, methyl 5-phenyl-3,4-dithiapentanoate (I), " ΔpK_a " 1.63,⁵ provided a 53.8% yield of the more stable mercaptide, sodium carbomethoxymethyl mer-

captide (III) (isolated as the N,N-diphenylthiocarbamate derivative IV), 43.7% of the corresponding thiocyanate II, and 4.2% of methyl thiocynoacetate (V). A similar cleavage of methyl 3,4-dithiadecanoate



(VI), " ΔpK_a " 2.86, gave only the more stable mercaptide III (also isolated as IV) and *n*-hexyl thiocyanate.



The results⁴ obtained from the cyanide cleavage reactions using N,N-diphenylcarbamyl chloride (DPCC) were in agreement with the previous^{3,6} conclusion that the bond-breaking step in nucleophilic cleavage of the sulfur-sulfur bond, rather than the bond-forming step, is of major importance. Since the scavengers used were presumably efficient mercaptide traps, these results implied that initial nucleophilic attack on an unsymmetrical disulfide occurred on the more electron-dense sulfur. Thus the more stable mercaptide ion was displaced. However, several

(1) Supported by research grant RG-7968 from the National Institute of General Medical Sciences of the National Institutes of Health, United States Public Health Service.

(2) Part VI of this series: R. G. Hiskey, W. H. Bowers, and D. N. Harpp, *J. Am. Chem. Soc.*, **86**, 2010 (1964).

(3) A. J. Parker and N. Kharasch, *ibid.*, **82**, 3071 (1960).

(4) R. G. Hiskey and F. I. Carroll, *ibid.*, **83**, 4644 (1961).

(5) The " ΔpK_a " value of a symmetrical disulfide is zero.

(6) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

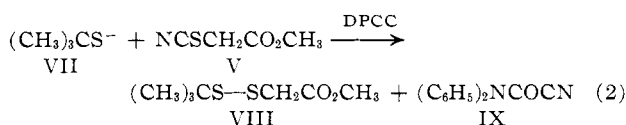
TABLE I
CYANIDE ION CLEAVAGE OF DISULFIDES IN THE PRESENCE OF ALKYL OR ARYL THIOCYANATES^a

$$-\text{CN} + \text{RS}-\text{SR}' \xrightleftharpoons[\text{NCSR}']{\text{R}''\text{SCN}} \text{RS}^- \xrightleftharpoons{\text{R}''\text{SCN}} \text{RS}-\text{SR}'' + -\text{CN}$$

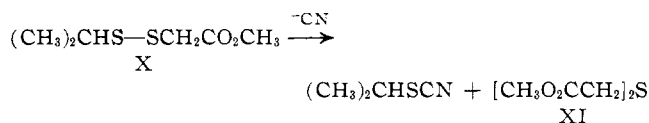
Expt.	Disulfide RS-SR'	Scavenger R''SCN	% Recovd. RS-SR'	% Recovd. scavenger	% Scavenged mercaptide RSSR''	% Recovd. NaCN	% R'SCN	% RSCN
A	(CH ₃) ₃ CSSCH ₂ CO ₂ CH ₃ (VIII), ΔpK _a 3.25	None	86.0			90.1		9.5
B	(CH ₃) ₃ CSSCH ₂ CO ₂ CH ₃	C ₆ H ₅ CH ₂ SCN	43.7 21.6 ^c	45.6 20.8	47.6 59.4	83	0 ^b	8.9
C	(CH ₃) ₃ CSSCH ₂ CO ₂ CH ₃	C ₆ H ₅ SCN	39.8	33.3	44.8	71	0 ^b	
D	(CH ₃) ₃ CSSC ₆ H ₅ (XVI), ΔpK _a 4.55	C ₆ H ₅ CH ₂ SCN	74.3	59.7	18.8	77	10.1	
E	(CH ₃) ₃ CSSCH ₂ CH ₂ CH ₃ (XVII), ΔpK _a 0.57	C ₆ H ₅ SCN	33.0	23.4	61.4	76	51.6	

^a Unless otherwise noted the reaction conditions used were: acetonitrile solvent, 50°, 11 hr. ^b Trace amounts detected in the vapor fractogram. ^c Values obtained after 70 hr.

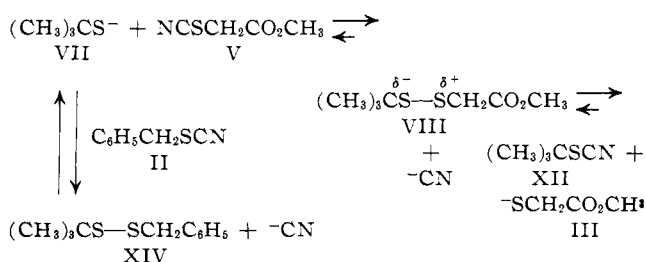
subsequent experiments suggested that DPCC was not an efficient mercaptide scavenger. For example, the reaction of *t*-butyl mercaptide (VII) with V in the presence of DPCC afforded methyl 5,5-dimethyl-3,4-dithiahexanoate (VIII) in 89.5% yield.² A 70% yield of N,N-diphenylcarbonyl nitrile (IX) was also obtained. This observation indicated that the reverse reaction, formation of V and VII from VIII and cyanide ion, would not be detected if it occurred. Furthermore,



the production of the symmetrical sulfide dimethyl 3-thiaglutarate (XI) from cleavage of methyl 5-methyl-3,4-dithiahexanoate (X) in the absence of DPCC suggested² initial attack of cyanide ion might occur on the more positively polarized sulfur atom of X.



The unsymmetrical disulfide VIII was selected as the substrate for cleavage experiments designed to determine the extent, if any, of nucleophilic attack on the more positively polarized sulfur atom of an unsymmetrical disulfide. Attack of cyanide ion on the *t*-butyl sulfur atom of VIII, to provide the more stable mercaptide III and *t*-butyl thiocyanate (XII), was known to be retarded.² Thus, initial attack on the more positively polarized sulfur atom of VIII might be more readily detected. However, attack of this type was not detected when VIII was treated with cyanide and DPCC and, therefore, a more efficient mercaptide scavenger was desired. Since the reaction

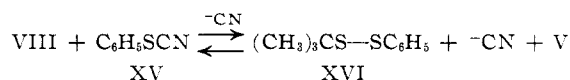


shown in eq. 2 suggested a thiocyanate was a more efficient scavenger than DPCC, the cyanide cleavage of VIII was conducted in the presence of benzyl thiocyanate (II).

It was anticipated that II would compete effectively with methyl thiocynoacetate (V) for any *t*-butyl mercaptide (VII) formed and that a mixture of VIII, V, II, and a new unsymmetrical disulfide, 4,4-dimethyl-1-phenyl-2,3-dithiapentane (XIV), would be obtained. Analysis of the reaction mixture in the vapor fractometer after 11 hr. indicated the presence of 47.6% XIV, 45.3% II, and 43.7% of recovered VIII (Table I). A separate reaction analyzed at intervals for 70 hr. (Table III) indicated that relatively constant values of 60% XIV, 21% II, and 22% VIII were reached in about 23 hr. Analysis for *t*-butyl thiocyanate (XII) after 70 hr. indicated the presence of 9%, a value in good agreement with the amount of XII produced from cyanide cleavage of VIII in the absence of a scavenger.

Although a peak due to methyl thiocynoacetate (V) was always present in the vapor fractograms of the reaction mixture, the peak area was very small. Incubation of V with cyanide ion indicated that under the conditions employed for the reaction and analysis only 29.2% of V could be detected. The fact that constant values of the other volatile components were obtained in 23 hr. suggest that V does not decompose to a major extent in the cleavage reaction. It was established that pure V gave a low response under the conditions used for the analysis. Therefore, the small peak areas may arise from either low detector response or decomposition during analysis.

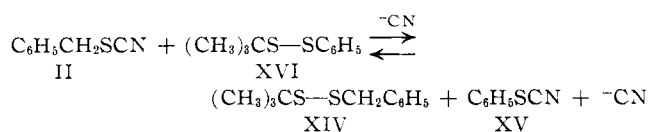
Similar results were obtained from the cleavage of VIII in the presence of phenyl thiocyanate (XV). The scavenged mercaptide VII was obtained as 1-phenyl-3,3-dimethyl-1,2-dithiabutane (XVI) in 44.8% yield. Although the thiocyanate V was present in the



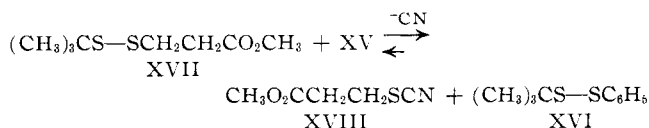
vapor fractogram, the peak area was again very small.

A reasonable recovery of the thiocyanate formed from disulfide cleavage was obtained from the reaction of XVI with cyanide using II as a scavenger. Analysis of the reaction mixture in the vapor fractometer

showed the presence of 18.8% of the trapped product XIV, 10.1% of phenyl thiocyanate (XV), and 74.3% of recovered XVI.

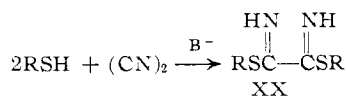
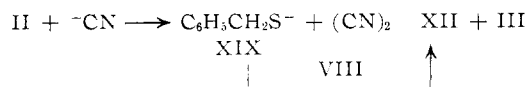


These data suggest that XV is a more effective mercaptide scavenger than II. Thus, if a thiocyanate (produced by disulfide cleavage) was a much less effective mercaptide scavenger than the added thiocyanate (II or XV), larger amounts of the trapped mercaptide VII should result. To test this possibility methyl 6,6-dimethyl-4,5-dithiaheptanoate (XVII) was cleaved in the presence of XV. As predicted, a larger percentage (61.4%) of trapped product XVI was obtained. In addition a 51.6% yield of methyl β -thiocyanopropionate (XVIII), the thiocyanate formed by cleavage, was detected.



Although the results of the cleavage reactions (summarized in Table I) are consistent with attack of cyanide ion on the more positively polarized sulfur atom to yield the less stable mercaptide, several alternative explanations are possible. Therefore, experiments designed to distinguish between the various possibilities were initiated.

When VIII and II were allowed to react in the absence of cyanide ion, no cleavage occurred and quantitative recoveries of the reactants were obtained. Thus, cyanide ion is required for reaction to occur. The disulfide XIV can conceivably be produced from either VII and II, as proposed, or from *t*-butyl thiocyanate (XII) and benzyl mercaptide (XIX). Another possibility would be the generation of XIV by attack of XIX on the *t*-butyl sulfur atom of VIII. Therefore, the possibility of benzyl mercaptide formation was considered in detail. Benzyl mercaptide could be generated from the reaction of cyanide ion and II as shown below; however, a control reaction using II and cyanide ion resulted in 92% recovery of II. Further-

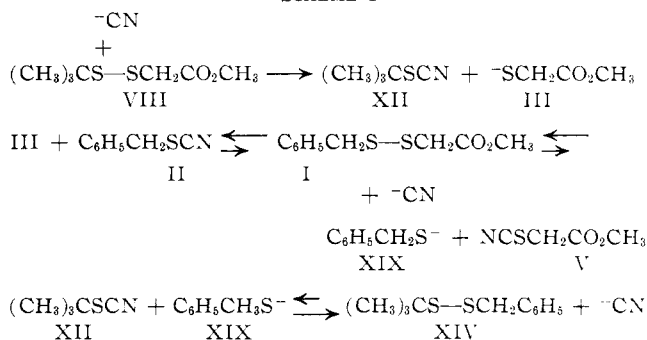


more, if II decomposed in this manner to yield XIX and cyanogen, the latter would be expected to react with XIX or another mercaptide to yield the dithiooxaldimic ester⁷ XX. This would require the consumption of cyanide ion whereas, in fact, cyanide was recovered in 83% yield from the cleavage of VIII in the presence of II.

If cleavage of VIII occurred by attack of cyanide on the *t*-butyl sulfur atom to yield the more stable mercaptide III (Scheme I), the mercaptide might be ex-

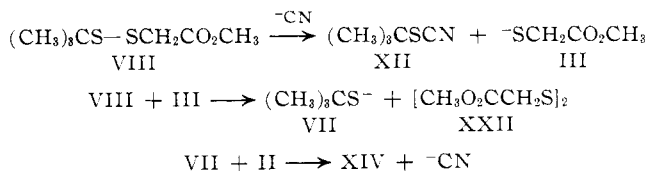
pected to react with II to produce methyl 5-phenyl-3,4-dithiapentanoate (I). The cyanide cleavage of I

SCHEME I



in the presence of DPCC was previously shown to afford mainly the more stable mercaptide III (as the derivative IV) and II. However, a 4.2% yield of the thiocyanate V was obtained and thus XIX was undoubtedly present. Therefore, it could be argued that XIX would react with XII to provide XIV, the observed trapped mercaptide. The reactions in Scheme I imply that *t*-butyl thiocyanate (XII) is able to compete successfully with II for the mercaptide XIX. Intuitively, however, it might be expected that most of the benzyl mercaptide (XIX) formed would react with benzyl thiocyanate (II) to produce benzyl disulfide (XXI). To test this possibility equimolar quantities of II, XII, and XIX were allowed to react under the standard conditions. Analysis of the reaction mixture indicated 77.8% of XXI, 3.0% XIV, and 73% recovered XII resulted. Thus, the equilibria shown in Scheme I would not be expected to yield XIV but rather the symmetrical disulfide XXI.

Another possible explanation for the formation of XIV, other than by nucleophilic attack of cyanide ion on the more positive sulfur atom of VIII, would involve the reaction of III with VIII to yield dimethyl dithiodiglycolate (XXII) and VII. The reaction of VII and II would provide XIV. This route would predict sizable amounts of XII and XXII to result.



However, the vapor fractograms of the reaction mixture showed no peak due to XXII and only small quantities of XII were present after 11 hr.

The most reasonable explanation of the results would, therefore, involve *initial attack of cyanide ion on the more positively polarized sulfur atom of the unsymmetrical disulfide*. This attack would provide the *less stable mercaptide and corresponding thiocyanate as the initial cleavage products*. The results in Table I can then be explained by assuming that competition between the thiocyanate formed by cleavage and the added thiocyanate favors the more reactive of the two.

Since the disulfides studied have contained a *t*-butyl group (known to retard formation of the more stable mercaptide), no decision can be made regarding the generality of these results. However, cleavage of at least some unsymmetrical disulfides with cyanide

(7) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 371 (1952).

ion, and probably other nucleophiles, clearly involves two steps: (a) A rapid, reversible equilibrium between the starting disulfide and the least stable products (mercaptide of greater pK_a value) resulting from nucleophilic attack on the more positively polarized sulfur atom of the disulfide bond. This step is followed by (b) a slower more irreversible step favoring the more stable cleavage products (mercaptide of lower pK_a). If the relative stability of the two mercaptides are similar, a mixture of the four possible primary cleavage products would result as previously demonstrated⁴; however, presumably initial attack would still occur on the more positively polarized sulfur atom of the unsymmetrical disulfide.

Experimental⁸

Methyl 5,5-dimethyl-3,4-dithiahexanoate (VIII) and 1-phenyl-4,4-dimethyl-2,3-dithiapentane (XIV) were prepared as previously⁹ described.

1-Phenyl-3,3-dimethyl-1,2-dithiabutane (XVI) was prepared in 76% yield by the sulfonyl thiocyanate method⁹; b.p. 73–75° at 0.3 mm., n_D^{25} 1.5728, d_4^{25} 1.0548; MR calcd. 61.26, found 61.94. Anal. Calcd. for $C_{10}H_{14}S_2$: C, 60.55; H, 7.11; S, 32.33. Found: C, 60.34; H, 7.14; S, 32.33.

Methyl 6,6-dimethyl-4,5-dithiaheptanoate (XVII) was prepared in 58% yield by the sulfonyl thiocyanate method⁹; b.p. 65° at 0.02 mm., n_D^{25} 1.4960, d_4^{25} 1.0761; MR calcd. 56.80, found 56.64.

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.37; H, 7.74; S, 30.78. Found: C, 46.37; H, 7.73; S, 30.95.

Methyl β -thiocyanopropionate (XVIII) was prepared as previously described.⁴

Phenyl thiocyanate (XV) was prepared in 34% yield by the procedure of Söderbäck¹⁰; b.p. 78–79° at 1.8 mm., reported¹⁰ 71–73° at 1.5 mm.

Dimethyl 3-thioglutarate (XI) was prepared by the action of sodium carbomethoxymethyl mercaptide (III) on methyl α -chloroacetate; b.p. 93° at 0.4 mm., n_D^{25} 1.4740, d_4^{25} 1.2244; MR calcd. 40.92, found 40.90; reported¹¹ b.p. 135° at 11 mm.

Purification of Acetonitrile.—The acetonitrile employed as a solvent for all cleavage or recombination reactions was purified according to method D-1 of Coetzee, *et al.*¹²

Cyanide Cleavage of Unsymmetrical Disulfides in Acetonitrile Using Phenyl or Benzyl Thiocyanate. A. Chromatography Conditions.—Vapor phase chromatograms were obtained on a F and M Model 500 fractometer (Honeywell recorder) using 22-in., 4-mm. glass columns packed with (a) 4.0% Carbowax 400 on Chromosorb P (60/80 mesh) as a polar column and (b) 10% silica Dow 710 on Chromosorb P¹³ (60/80 mesh) as a nonpolar column. The reaction mixtures were analyzed using both columns. The yields of the volatile cleavage products were obtained from standard calibration curves of each pure component. Ethyl benzoate, benzyl thiocyanate, and N,N-diphenylcarbonyl chloride were used as internal standards. The calibration data and retention times of the various products are shown in Table II.

B. Cyanide Cleavage Conditions. Methyl 5,5-Dimethyl-3,4-dithiahexanoate (VIII) in the Presence of Benzyl Thiocyanate (II).—A stirred solution containing 0.245 g. (0.005 mole) of finely powdered dry sodium cyanide and 0.745 g. (0.005 mole) of II in 100 ml. of purified acetonitrile was treated with a solution containing 0.97 g. (0.005 mole) of VIII in 150 ml. of acetonitrile. The addition required 0.5 hr. The mixture was maintained at 50 \pm 1° under a nitrogen atmosphere for 11 hr. The solution was cooled in an ice bath for 15 min., filtered, and the recovered sodium cyanide dried at 45–55°.

The acetonitrile solution was concentrated to a viscous oil and triturated with 5–10 ml. of anhydrous ether. The precipitated

TABLE II
VAPOR CHROMATOGRAPHY CONDITIONS FOR CALIBRATION
CURVES^a

Compound	Stand- ard	Column temp., °C.	Retention time, ^b —sec.—	
			Col- umn 1 ^c	Col- umn 2 ^d
(CH ₃) ₃ CSSC ₆ H ₅ (XVI)	a ^e	135	380	445 ^h
(CH ₃) ₃ CSSCH ₂ C ₆ H ₅ (XIV)	a	135	854	
(CH ₃) ₃ CSSCH ₂ CO ₂ CH ₃ (VIII)	a	135	310	262 ^h
(CH ₃) ₃ CSSCH ₂ CH ₂ CO ₂ CH ₃ (XVII)	a	135	485	
CH ₃ O ₂ CCH ₂ SSCH ₂ CO ₂ CH ₃ (XXII)		180		314
C ₆ H ₅ CH ₂ SSCH ₂ C ₆ H ₅ (XXI)	c ^g	225		440
CH ₃ O ₂ CH ₂ SSCH ₂ CO ₂ CH ₃ (XI)	a	135	636	
(CH ₃) ₃ CSCN XII	a	95	96	
C ₆ H ₅ SCN (XV)	a	135	310	173 ^h
C ₆ H ₅ CH ₂ SCN (II)	a	135	1349	
CH ₃ O ₂ CCH ₂ SCN (V)	a	135	514	131 ^h
CH ₃ O ₂ CCH ₂ CH ₂ SCN (XVIII)	a	135	637	
(C ₆ H ₅) ₂ NCOCl (DPCC)	b ^f	200		545
(C ₆ H ₅) ₂ COCN (IX)	b	200		707

^a All calibration curves were obtained at a column flow rate of 60 ml. of helium/min. and a detector flow rate of 18–24 ml. of helium/min. ^b Retention times given were obtained from the calibration solution of the particular compound. The retention times were found to vary from run to run; however, the times were internally consistent relative to the pure component. ^c Column 1, 4.0% Carbowax 400 on Chromosorb P (60/80 mesh). ^d Column 2, 10% silica Dow 710 on Chromosorb P (60/80 mesh). ^e Ethyl benzoate. ^f Benzyl thiocyanate. ^g N,N-Diphenylcarbonyl chloride. ^h These retention times were obtained using a column temperature of 160°.

solids were collected. The remaining clear orange-red oil was reconcentrated¹⁴ and analyzed in the vapor fractometer.

The formation of XIV and the disappearance of VIII were followed as a function of time in a similar reaction. Aliquots (1.0 ml.) were withdrawn, concentrated, and analyzed for II, VIII, and XIV. The results are shown in Table III.

TABLE III
VOLATILE PRODUCTS FROM CYANIDE CLEAVAGE OF VIII IN THE
PRESENCE OF II

Time, hr.	% VIII	% XIV	% II	Ratio XIV:VIII
2.5	56.8	27.6	55.2	0.49
11	48.2	37.8	48.6	0.79
47	23.2	60.3	22.8	2.6
70	21.6	59.4	20.8	2.7
94	20.5	54.2	17.6	2.6

Cleavage of Methyl 5,5-Dimethyl-3,4-dithiahexanoate (VIII) with Cyanide Ion.—A solution containing 0.005 mole of VIII and 0.005 mole of powdered sodium cyanide in 250 ml. of acetonitrile was allowed to react using the conditions previously described. Treatment of the reaction mixture with ether provided 90.1% of recovered sodium cyanide. Analysis of the reaction mixture in the vapor fractometer indicated the presence of 86.0% recovered VIII and 9.5% of XII.

Reaction of Thiocyanates with Cyanide Ion.—In separate experiments equimolar quantities of methyl thiocyanacetate (V), phenyl thiocyanate (XV), and benzyl thiocyanate (II) were allowed to react with sodium cyanide. The reaction conditions were those employed previously. Analysis of the reaction mixtures containing V and XV in the vapor fractometer indicated only a single volatile component was present. The peak areas indicated a 29.0% recovery of V and a 90.7% recovery of XV. A 92.1% recovery of II was obtained by crystallization.

Reaction of Methyl 5,5-Dimethyl-3,4-dithiahexanoate (VIII) and Benzyl Thiocyanate (II).—A solution containing 0.323 g. (1.67 mmoles) of VIII and 0.248 g. (1.67 mmoles) of II in 82 ml. of acetonitrile was stirred under nitrogen for 14 hr. at 50°.

(14) In some experiments XII was found to be present in the solvent obtained from concentration of the reaction mixture. Thus the analysis was conducted on both the concentrated reaction mixture and the recovered solvent.

(8) Melting points and boiling points are uncorrected. Elemental analyses by Micro-Tech Laboratories, Skokie, Ill.

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

(10) E. Söderbäck, *Acta Chem. Scand.*, **8**, 1851 (1954).

(11) R. Anschütz and R. Birnaux, *Ann.*, **273**, 64 (1893).

(12) J. F. Coetzee, G. P. Cunningham, D. K. McGuire, and G. R. Padmanabhan, *Anal. Chem.*, **34**, 1139 (1962).

(13) We wish to acknowledge valuable discussions with Dr. G. P. Hildebrand concerning the use of this system.

Analysis of an aliquot in the vapor fractometer indicated the presence of $100 \pm 3\%$ of each component. No other volatile components were present.

Reaction of Sodium Benzyl Mercaptide (XIX) with Benzyl Thiocyanate (II) and *t*-Butyl Thiocyanate (XII).—To a solution containing 0.805 g. (0.0054 mole) of II and 0.623 g. (0.0054 mole) of XII (in a 1.280-g. mixture of 48.7% *t*-butyl thiocyanate and 51.3% *t*-butyl isothiocyanate) in 40 ml. of acetonitrile was added 0.788 g. (0.0054 mole) of freshly prepared XIX in 40 ml. of acetonitrile. The reaction mixture was kept under a nitrogen atmosphere with magnetic stirring at 50° for 11 hr. The red-orange mixture was cooled, filtered, and the sodium cyanide dried to a constant weight, 0.252 g. (91.5%). The filtrate was

concentrated *in vacuo* and triturated with 8 ml. of dry methanol. The benzyl disulfide (XXI) obtained, 0.950 g. (70.3%), melted at $66\text{--}68^\circ$. A mixture melting point with an authentic sample melted at $67\text{--}69^\circ$.

The residue was analyzed in the vapor fractometer using column 2 and contained 7.2% XXI (total yield 77.5%). Analysis of the oil on column 1 showed the presence of 3.0% 1-phenyl-4,4-dimethyl-2,3-dithiapentane (XIV). The vapor fractogram exhibited three additional components of small peak areas which were not identified.

Acknowledgment.—Preliminary experiments on this work were performed by Mr. William H. Bowers.

[CONTRIBUTION FROM THE ESSO RESEARCH AND ENGINEERING CO., PROCESS RESEARCH DIVISION, EXPLORATORY RESEARCH SECTION, LINDEN, N. J.]

Reactions of Thiols with Sulfoxides. I. Scope of the Reaction and Synthetic Applications

BY THOMAS J. WALLACE

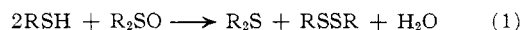
RECEIVED DECEMBER 14, 1963

A detailed study on the oxidation of thiols by sulfoxides has been made. The reaction products are disulfides and sulfides (reduced sulfoxides). Of the sulfoxides investigated, dimethyl sulfoxide and tetramethylene sulfoxide were found to be the most efficient oxidizing agents. The reaction takes place with aliphatic, aralkyl, and aromatic thiols. The order of thiol reactivity was $\text{ArSH} > \text{ArCH}_2\text{SH} > \text{RSH}$. It was also possible to oxidize dithiols by this technique. Thus 1,4-butanedithiol and 1,3-propanedithiol were oxidized to their corresponding 1,2-dithianes. Some limited mechanistic implications are presented and discussed based on the results obtained. Stoichiometrically, it has been established that 2 moles of thiol reacts with 1 mole of sulfoxide to produce 1 mole of disulfide and 1 mole of sulfide. Synthetically, it appears that aromatic thiols are selectively oxidized to their disulfides at room temperature by dimethyl sulfoxide and tetramethylene sulfoxide.

Introduction

Oxidation-reduction reactions involving sulfoxides have been observed with a wide variety of reagents. For example, reduction of dimethyl sulfoxide (DMSO) to dimethyl sulfide occurs in the presence of hydrogen halides, bromine, organic halides, and higher aliphatic sulfides.¹ More recently, it has been found that 1,4-diols can be dehydrated and cyclized to tetrahydrofuran derivatives by adding the diol to a refluxing solution of DMSO.² The above results¹ have established that sulfoxides are weak bases¹ that are capable of oxidizing a variety of acidic (protic) species. In the past few years, we have been interested in the reactions of thiols with a variety of bases.^{3,4} A thorough search of the literature revealed that thiol-sulfoxide reactions have not previously been investigated in detail.⁵ During the preparation of the present manuscript, Yiannios and Karabinos^{5b} reported that DMSO is capable of oxidizing a large number of acidic thiols. These oxidation studies were carried out at $80\text{--}90^\circ$ for 8 hr. in the presence of air. These authors also indicate that α -

toluenethiol and 1-butanethiol are oxidized at the same rate as acidic (ArSH) thiols. Oxidation of benzenethiol by DMSO under nitrogen for 18 hr. produced the same yield of disulfide obtained after 8 hr. of oxidation in the presence of air. Based on this result, Yiannios and Karabinos^{5b} concluded that co-oxidation of the thiol by air did not occur. In the present paper, we wish to report the results of our initial studies on thiol-sulfoxide reactions under nitrogen. Theoretically, an interaction between the two species should yield sulfide, disulfide, and water. This possibility was investigated and found to be true. Under our experimental conditions, it has



been found that the rate of reaction is markedly dependent on the acidity of the thiol. A variation of the reaction temperature has revealed that acidic thiols can be oxidized conveniently at room temperature. It has also been ascertained that, in the absence of air, oxidation of aliphatic thiols at reasonable rates requires temperatures in excess of 100° . In the present paper, the scope, synthetic application, and limitation of various thiol-sulfoxide reactions will be presented.⁶ In a following paper, the kinetic and mechanistic aspects of these reactions will be discussed.

Results

The reaction of thiols with sulfoxides has been investigated under a wide variety of conditions. Reactions were carried out under nitrogen in a micro scale reaction flask equipped with a Vigreux distilling column. In most reactions, an excess of sulfoxide to thiol was employed. In order to simplify the analytical procedure for separating and identifying reaction products,

(1) For a summary see: W. O. Ranky and D. C. Nelson, "Organic Sulfur Compounds," Vol. I, ed. by N. Kharasch, Pergamon Press, New York, N. Y., 1961, Chapter 17.

(2) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

(3) T. J. Wallace, H. Pobiner, and A. Schriesheim, *ibid.*, **29**, 1044 (1964).

(4) T. J. Wallace, N. Jacobson, and A. Schriesheim, *Nature*, **201**, 609 (1964).

(5) (a) One remotely related study is that of Bunnett and co-workers: J. F. Bunnett, E. W. Garbish, and K. U. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957). In a study on activated nucleophilic aromatic substitution reactions these workers found that 2,4-dinitrophenyl phenyl sulfide and phenyl disulfide were by-products of a reaction between 2,4-dinitrophenyl phenyl sulfoxide and piperidine. A detailed study on the mechanism of sulfide and disulfide formation was not undertaken, but it is possible that they could have arisen by an oxidation-reduction reaction involving the thiol anion and the sulfoxide. (b) A study on the reaction of DMSO with acidic thiols has recently been reported: C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).

(6) For a preliminary account see T. J. Wallace, *Chem. Ind. (London)*, 504 (1964).