

TABLE I

$$\begin{array}{c} \text{N}\equiv\text{CCH}-\text{CHC}\equiv\text{N}^a \\ | \quad | \\ \text{R}' \quad \text{R}'' \end{array}$$

R	R''	Yield, %	M.p., °C. ^b		Carbon, %		Hydrogen, %	
			Crude	Recrystd.	Calcd.	Found	Calcd.	Found
C ₆ H ₅	C ₆ H ₅ ^c	77-87	204-205	238-239				
C ₆ H ₅	<i>p</i> -ClC ₆ H ₄ ^d	81	203	228-229	72.04	72.22	4.16	4.15
<i>p</i> -ClC ₆ H ₄ ^e	C ₆ H ₅	60	193-195	226-228				
<i>p</i> -OCH ₃ C ₆ H ₄	C ₆ H ₅ ^f	69	181-182	203-205 ^g				
<i>p</i> -OCH ₃ C ₆ H ₄	<i>p</i> -ClC ₆ H ₄	54	186-188	222-224	68.80	68.58	4.41	4.48
<i>p</i> -ClC ₆ H ₄ ^h	<i>p</i> -ClC ₆ H ₄	65	196-199	234-236	63.80	63.96	3.35	3.16
C ₇ H ₅ O ₂ ⁱ	C ₆ H ₅	54	185-188	218-220	73.90	74.31	4.38	4.45
<i>n</i> -C ₈ H ₇	C ₆ H ₅	30	88-94	94-97	78.75	78.98	7.12	7.16 ^j
<i>p</i> -(<i>i</i> -C ₃ H ₇)C ₆ H ₄	C ₆ H ₅	58	197-200	204-206	83.18	83.37	6.61	6.56 ^k

^a R' is from an aldehyde, R'CH=O. R'' is from an arylmethylene cyanide, R''CH₂CN. ^b Melting points are uncorrected. ^c Benzyl chloride in place of benzyl cyanide gave 80% yield. ^d *p*-Chlorobenzyl chloride in place of *p*-chlorobenzyl cyanide gave 42% yield. ^e The reagents were mixed at room temperature. The mixture was then heated slowly to 55°. ^f Benzyl chloride in place of benzyl cyanide gave 65% yield. ^g Lit. value 204°; J. A. McRae and A. S. Townshend, *C. A.*, 29, 1078 (1935). ^h Reaction temperature 45-55°. ⁱ 3,4-Methylenedioxyphenyl. ^j Nitrogen, calcd. 14.13, found 14.20. ^k Nitrogen, calcd. 10.21, found 10.25.

of 80% methanol and drying under vacuum gave 101 g. (87%) of solid, m.p. 202-205°, recrystallized from acetic acid, m.p. 235-237°.

D.—A mixture of 111 g. of sodium cyanide, 100 ml. of water and 500 ml. of absolute methanol was heated to gentle reflux. Then 40 g. of benzyl chloride was added dropwise over 15 minutes with vigorous stirring. A mixture of 90 g. of benzyl chloride and 53 g. of benzaldehyde was added over 35 minutes at gentle reflux with vigorous stirring.⁵ The reaction mixture was refluxed for one hour with vigorous stirring, allowed to cool and was filtered. The solid was washed well with 70% methanol, water, 70% methanol and ether, and then air-dried. The solid weighed 93 g. (80%

yield), m.p. 203-206°, recrystallized from acetic acid, m.p. 235-236°.

Preparation of 2-Phenyl-3-propylsuccinonitrile.—To a mixture of 50 ml. of water, 49 g. of sodium cyanide, 250 ml. of absolute methanol and 15 g. of benzyl cyanide, heated to 35-40°, was added with stirring over 4 hours a mixture of 24 g. of benzyl cyanide, 21.6 g. of butyraldehyde and 200 ml. of absolute methanol. The reaction mixture was then heated at 35-40° with stirring for one additional hour. Two liters of water was added and the mixture extracted four times with 300-ml. portions of ether. The combined extracts were washed with water and dried over potassium carbonate. The ether was removed by distillation, 200 ml. of fresh ether was added, and the mixture was placed in the refrigerator overnight, during which time solid precipitated. The mixture was filtered and the solid washed with 70% methanol. The solid, 18 g. (30% yield), melted at 88-94°, recrystallized from ethanol, m.p. 94-97°.

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[CONTRIBUTION FROM THE PHYSIOLOGY DIVISION, CHEMICAL WARFARE LABORATORIES]

Formation of Thiocyanate Ion through Neighboring Group Displacement Reactions

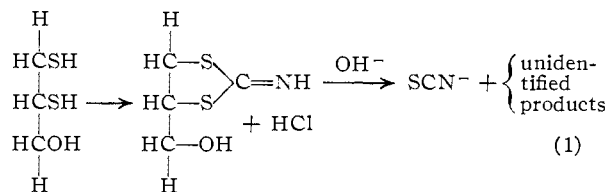
By JOEL R. SIEGEL¹ AND DAVID H. ROSENBLATT

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A general mechanism is proposed for the release of thiocyanate ion from vicinal and geminal aliphatic dithiocyanates, β-mercaptoaliphatic thiocyanates and 2-imino-1,3-dithiolanes on treatment with base. The series of reactions whereby the aqueous solution of a vicinal dithiol is treated with cyanogen chloride and then made basic to release thiocyanate ions is discussed in the light of the general mechanism.

The interest of these laboratories in the chemistry of 2,3-dimercapto-1-propanol (BAL), which is used as an antidote for arsenical and heavy metal poisoning, occasioned an inquiry into the nature of the initial steps in Aldridge's method² for determining aliphatic vicinal dithiols. This method entails estimation of the thiocyanate ion liberated when a vicinal dithiol is treated with cyanogen chloride and made alkaline; it is rather specific and very sensitive, but tedious, exacting and time-consuming. It occurred to us that there might be found a simpler, if less sensitive, means of estimating the postulated intermediate, 2-imino-4-hydroxy-

methyl-1,3-dithiolane,² if additional evidence should confirm Aldridge's hypothesis, namely

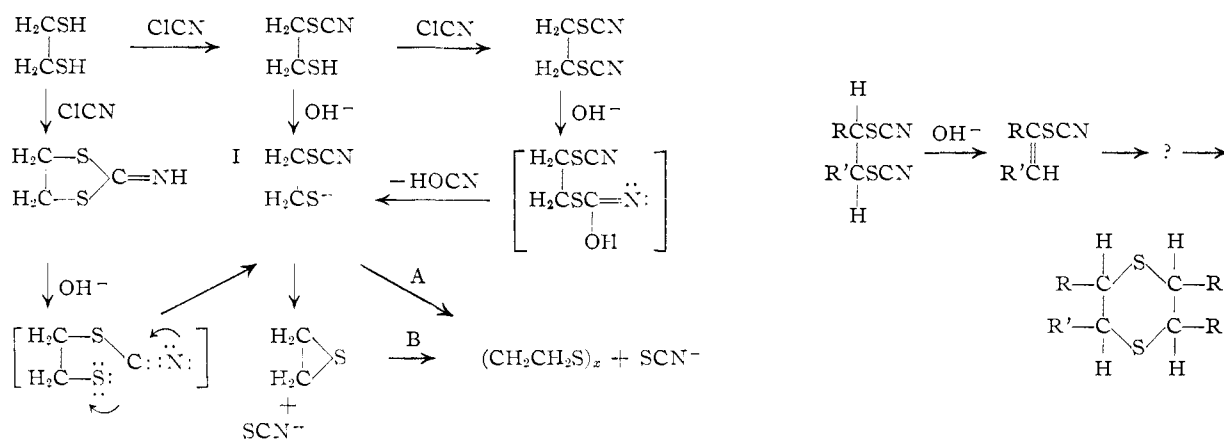


Although simple organic thiocyanates commonly react with base to give mercaptide ions and cyanate, with disulfides as end products,³ examination of

(1) Esso Research and Engineering Co., Linden, N. J.

(2) W. N. Aldridge, *Biochem. J.*, 42, 52 (1948).

(3) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, 49, 1 (1951).



the literature and our own experiments revealed the existence of thiocyanate derivatives capable of producing thiocyanate ion on treatment with base. Thus, Hagelberg⁴ demonstrated the formation of thiocyanate ion from the reaction of propylene dithiocyanate with sodium hydroxide. Similarly, Kaufmann and co-workers⁵ reported the production of one mole of thiocyanate ion, and one mole of cyanate ion when a mole of vicinal dithiocyanate, obtained by the addition of thiocyanogen to the double bond of an unsaturated fatty acid, was treated with sodium hydroxide. This result was confirmed, in the present study, by qualitative experiments on ethylene dithiocyanate. In these experiments we noted in addition, however, the odor of ethylene sulfide, and observed the formation of ethylene sulfide polymer. The geminally substituted methylene dithiocyanate and 2-mercaptoethyl thiocyanate, in the form of its copper salt, likewise released thiocyanate ion when treated with base. In accord with Aldridge's hypothesis, 2-imino-1,3-dithiolane hydrochloride also liberated thiocyanate ion when it was made basic. Cysteine, which under Aldridge's conditions² failed to liberate thiocyanate ion, was found to do so at high concentrations.

We have carried out the reaction of cyanogen chloride with ethanedithiol at high concentrations to form ethylene dithiocyanate,⁶ which can therefore represent a possible intermediate in the transition from vicinal dithiol plus cyanogen chloride to thiocyanate ion.

Although a plausible mechanism is not evident to explain the necessary formation of the imino-dithiolane (which finds a parallel in the synthesis of 2-aminobenzothiazole from cyanogen chloride and 2-mercaptoaniline⁷) the role of this substance is supported by the experimental evidence.² However, if cyanogen chloride and base are added to the dithiol simultaneously, other routes to thiocyanate ion must be considered. The step leading to the formation of this ion may in each case be represented in terms of a neighboring group dis-

placement mechanism,⁸ in which the mercaptide I is the key intermediate. In the above scheme, A and B represent alternative paths to the ultimate products.

Certain difficulties with regard to the evolution of thiocyanate ion from organic compounds have been raised by the literature. Thus, the statement⁹ that 2-imino-1,3-dithiolane hydrochloride reacts with excess potassium carbonate to produce ethylene tetrasulfide precludes the mechanism of equation 1 since it accounts for all of the sulfur; our study indicates that the tetrasulfide is not formed. Despite the failure of simple organic thiocyanates to release thiocyanate ion when treated with alkali, Hagelberg⁴ reported the presence of this ion in the mixture resulting from the reaction of aqueous sodium hydroxide with trimethylene dithiocyanate; we have found this statement to be incorrect. Finally, the neighboring group displacement mechanism offers a more logical explanation of the reaction of base with vicinal aliphatic dithiocyanates than that proposed by previous authors,⁵ which involved an unsaturated organic thiocyanate intermediate.

Experimental

Ethylene dithiocyanate was prepared both by the reaction of potassium thiocyanate with ethylene dibromide¹⁰ and by the reaction of cyanogen chloride with 1,2-dimercaptoethane. In the latter method, 1 g. (0.0106 mole) of 1,2-dimercaptoethane and 4 ml. (excess) of cyanogen chloride were dissolved in 20 ml. of chilled 95% ethanol. To this solution, 2.26 g. (0.0212 mole) of sodium carbonate dissolved in 20 ml. of water was added rapidly with stirring. The resulting precipitate was isolated by filtration, washed with water and recrystallized from aqueous ethanol; m.p. 88.5°, mixed m.p. with material prepared by the first method, 88.5–90°.

2-Imino-1,3-dithiolane Hydrochloride.—The tin chloride double salt⁹ of 2-imino-1,3-dithiolane hydrochloride, made by heating ethylene dithiocyanate with stannous chloride and hydrochloric acid, was suspended in hot water and treated with hydrogen sulfide until the precipitation of tin sulfide was complete. After filtration, the solution was evaporated to dryness at reduced pressure on the steam-bath and the residue recrystallized from absolute ethanol, m.p. 207–209°, literature¹¹ m.p. 212°.

Other Compounds.—Methylene dithiocyanate, m.p. 102°, was prepared¹² from methylene iodide and potassium thio-

(4) L. Hagelberg, *Ber.*, **23**, 1083 (1890).

(5) H. P. Kaufmann, E. Gindberg, W. Rottig and R. Salchow, *ibid.*, **70**, 2519 (1937).

(6) This is similar to the reaction $RSNa + ClCN \rightarrow RSCN + NaCl$ of B. Abramovitch, U. S. Patent 2,486,090; *C. A.*, **44**, 2018 (1950).

(7) J. T. Cassaday and E. I. Hoegberg, U. S. Patent 2,575,614; *C. A.*, **46**, 6158 (1952).

(8) See, for example, R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946); C. C. Price and P. F. Kirk, *THIS JOURNAL*, **75**, 2396 (1953).

(9) A. Miolati, *Ann.*, **262**, 61 (1891).

(10) H. L. Buff, *Ann.*, **100**, 229 (1856).

(11) H. L. Wheeler and H. F. Merriam, *THIS JOURNAL*, **24**, 445 (1902).

(12) J. Lermontoff, *Ber.*, **7**, 1282 (1874).

cyanate. The copper salt of 2-mercaptoethyl thiocyanate¹³ was made by the reaction of the copper salt of acetoacetic ester with ethylene dithiocyanate in absolute ethanol. Trimethylene dithiocyanate⁴ was prepared from trimethylene dibromide and potassium thiocyanate. 2-Mercaptoethyl acetate,¹⁴ b.p. 62–66° (16 mm.), was made from 2-mercaptoethanol and acetic anhydride. Cysteine hydrochloride, 1,2-dimercaptoethane and 2-mercaptoethanol were commercial materials.

Tests for Thiocyanate Ion Evolution. (a) **Mercaptans.**—A small volume (about 3 ml.) of redistilled cyanogen chloride was added to a solution of about 0.1 g. of the substance to be tested in 2–3 ml. of water or ethanol–water. After a few minutes, the solution was made alkaline by the addition of aqueous sodium hydroxide (with care, in the case of cysteine hydrochloride, to raise the pH above 9). On acidification of the mixture and addition of a few drops of 5–30% aqueous ferric chloride solution, a deep red color indicated the presence of thiocyanate ions. Positive tests were obtained with 1,2-dimercaptoethane and cysteine hydrochloride, and a negative test with 2-mercaptoethanol.

(b) **Organic Thiocyanates and 2-Imino-1,3-dithiolane.**—The previously described procedure was followed with omission of the cyanogen chloride. Positive tests were obtained with ethylene dithiocyanate, methylene dithiocyanate, the copper salt of 2-mercaptoethyl thiocyanate and 2-imino-1,3-dithiolane, and a negative test with trimethylene dithiocyanate.

Identification of the Products of Reaction of Ethylene Dithiocyanate with Base. (a) **In Aqueous Ethanol.**—Ethylene dithiocyanate (0.1 g.) was dissolved in 25 ml. of 95% ethanol. Two milliliters of 0.2 *N* sodium hydroxide was added and the solution was allowed to stand two hours, after which 1 ml. of 6 *M* sulfuric acid was introduced. After addition of 20 ml. of water to the mixture, the precipitate was filtered off, dissolved in hot *N,N*-dimethylformamide and decolorized with a small amount of charcoal and diatomaceous filter aid.

(13) E. P. Kohler, *Am. Chem. J.*, **22**, 67 (1899).

(14) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952).

After filtration to remove the decolorizing agents, water was added until the hot solution became slightly cloudy. As the solution cooled, a precipitate formed which was reprecipitated in the same manner several times, until a constant melting point of 105–107° had been obtained. This substance gave an analysis close to that calculated for ethylene sulfide polymer. *Anal.* Calcd. for (C₂H₄S)₂: C, 40.0; H, 6.7; S, 53.3. Found: C, 39.4; H, 6.3; S, 53.1.

An authentic sample of ethylene sulfide polymer¹⁴ was made by dissolving 1 g. of 2-mercaptoethyl acetate in 5 ml. of absolute ethanol and adding 3 ml. of 20% sodium hydroxide. After one hour, a few ml. of water was added and the mixture was filtered. The solid thus obtained was precipitated several times from solution in *N,N*-dimethylformamide, as described in the preceding paragraph, and finally washed with ethanol and ether, m.p. 108–109°.

(b) **In Aqueous Acetone.**—Ethylene dithiocyanate (0.5 g.) was dissolved in 3 ml. of acetone. Three milliliters of 20% aqueous sodium hydroxide was added, the mixture was shaken well and 20 ml. of water was stirred in. After 15 minutes, the oily globules of ethylene sulfide that had formed were extracted with ether and the aqueous layer was separated and treated with 0.5 g. of semicarbazide hydrochloride in saturated aqueous solution. The pH was reduced to 8 by dropwise addition of dilute hydrochloric acid and the solution was permitted to stand several hours. The precipitate of hydrazodicarbonamide, a standard derivative for cyanate,¹⁵ was isolated by filtration and air-dried, m.p. 253–256°, literature¹⁶ m.p. 254–259°.

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(15) F. J. Welcher, "Organic Analytical Reagents," Vol. II, D. Van Nostrand Co., Inc., New York, N. Y., 1947, p. 454.

(16) N. A. Lange, "Handbook of Chemistry," 8th ed., Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 558.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WASHINGTON]

General vs. Specific Acid–Base Catalysis in Strong Mineral Acid Solution. Aromatic Decarbonylation¹

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Isotope effects have been determined for the decarbonylation of 2,4,6-triisopropylbenzaldehyde in 71–99% D₂SO₄–D₂O and for 2,4,6-triisopropylbenzaldehyde-*d*₁ (ArCDO) in 72–96% H₂SO₄–H₂O. The results are in complete agreement with the general acid–base catalysis mechanism of successive bimolecular proton transfer steps previously proposed. In accordance with expectation, based on steric grounds, a step involving proton transfer from solvent acids to the aromatic ring is rate controlling in the higher H₂SO₄ percentages and largely rate controlling in the lower H₂SO₄ percentages. Conclusions of general significance are: (1) general acid–base catalysis in non-dilute H₂SO₄ has been demonstrated; (2) agreement with the Hammett acid catalysis equation, $\log k_{\text{obsd}} + H_0 - \log ([B]/[B]_{\text{stoich}}) = \text{constant}$, over a limited acid range, is not a sufficient criterion for the assignment of mechanism; (3) the mechanism of successive bimolecular proton transfer steps assigned to the decarbonylation may give agreement with the Hammett equation under the condition that acid and/or basic catalysis constant ratios are the same as for indicator bases; (4) additional evidence that aromatic electrophilic substitution in general proceeds *via* an intermediate has been obtained.

The following bimolecular mechanism has been proposed for the replacement of the formyl group by hydrogen that occurs when 2,4,6-trialkylbenzaldehydes are treated with strong mineral acid (e.g., 60–100% H₂SO₄).^{3,4}

In these equations, HA_i refers to solvent acids (i.e., H₃O⁺ and H₂SO₄) and A_i refers to solvent bases (i.e., H₂O and HSO₄[−]), with the charges un-

specified. This mechanism was found to be consistent with all of the experimental facts amassed including the changes in *k*_{obsd} with percentage sulfuric acid for 2,4,6-trimethyl-, triethyl- and triisopropylbenzaldehyde, and the isotope effects for deuteromesitaldehyde (MesCDO) in 60–100% D₂SO₄–D₂O.⁴ Disagreement with the experimental facts was found for each of a number of other mechanisms considered, including the general Hammett mechanism and termolecular mechanisms.

In terms of this mechanism, the observed deuterium isotope effects with deuteromesitaldehyde

(1) Presented at the Symposium on Aromatic Substitution, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) Du Pont Pre-doctoral Fellow, 1956–1957.

(3) W. M. Schubert and R. E. Zahler, *THIS JOURNAL*, **76**, 1 (1954).

(4) W. M. Schubert and H. Burkett, *ibid.*, **78**, 64 (1956).