The Cyanoethylation of 2-Naphthol. Influence of Solvent and Concentration of Base[1]

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Received February 24, 1967

The reaction of 2-naphthol with acrylonitrile in the presence of sodium hydroxide was investigated in a variety of solvents. In aprotic solvents, the course of reaction was uninfluenced by the dielectric constant of the solvent employed. With equimolar sodium hydroxide as catalyst, carbon cyanoethylation was the predominant, or only, reaction. Oxygen cyanoethylation was favored by catalytic amounts of base. In protic solvents, the reaction was uneffected by the concentration of base; cyanoethylation at carbon predominated. Heterogeneity of the reaction mixture had little influence. Under comparable conditions, similar results were obtained with preformed sodium 2-naphthoxide.

Cyanoethylation, the Michael-type reaction of acrylonitrile, is widely used in synthesis.[3] With phenols, the base-catalyzed reaction generally yields the oxygen-cyanoethylated products, the β-cyanoethyl ethers.[4] In some cases, however, the phenoxide ions, as ambident anions, undergo cyanoethylation at carbon.[5,6] For example, when 2-naphthol is heated with excess acrylonitrile in the presence of a catalytic amount of Triton B, the ether β-(2-naphthoxy)propionitrile (I) (Scheme I) is produced.[7] On the other hand, the reaction of equimolar quantities of the naphthol, nitrile, and sodium hydroxide in benzene yields the carbon–cyanoethylation product, 1-(β-cyanoethyl)-2-naphthol (II).[6] The two experiments were repeated, and confirmed, by Lichtenberg[8] and co-workers in their study of the cyanoethylation of 2-naphthol. The results of these reactions were explained in terms of the polarity of the medium and homogeneity, or heterogeneity, of the mixture. Investigations of the reaction in other solvents were not reported.

Kornblum[9] and co-workers have investigated factors which influence the course of nucleophilic substitution reactions of phenoxide ions, and naphthoxide ion, with alkyl halides. The solvent[9c,d] was observed to play an important role in determining whether the reaction proceeded by oxygen or carbon alkylation, or in both ways. A similar study of the reaction of 2-naphthol with acrylonitrile was suggested to us by the work of Kornblum.

Results and Discussion

In Table I are summarized the results of experiments on the sodium hydroxide catalyzed reaction of 2-naphthol and acrylonitrile in benzene. With equimolar sodium hydroxide, the C-cyanoethylated compound (II) was the major product; with a catalytic amount of base, the O-cyanoethylated ether (I) was predominant. These observations are not in accord with those of Lichtenberg[8] who reported that progressive decrease in sodium hydroxide concentration to catalytic quantities resulted only in lower yields of II without the formation of any ether (I).

TABLE I

CYANOETHYLATION OF 2-NAPHTHOL IN BENZENE[a]

NaOH concn	Reflux time, hr	Yields of products, % I (O)	II (C)
Cat.[b]	2	4	1
Cat.	24	21	4
Cat.	48	23	1
Equimolar	1	8	36
Equimolar	2	4	47
Equimolar	24	0	60

[a] Equimolar (*ca.* 0.034 mole) 2-naphthol and acrylonitrile in 50 ml of benzene. [b] About 0.001 mole.

In these reactions in benzene, the yield of C-cyanoethylated product formed in the presence of equimolar base increased with reaction time, while the small amount of ether initially present disappeared. Lichtenberg reported that I was isomerized to II in 80–90% yields when heated for 2 hr with equimolar sodium hydroxide in benzene.[8] In view of this, it may appear that our reactions here are proceeding by an initial attack of acrylonitrile at the oxygen, followed by a base-catalyzed retro Michael, and eventual reaction at carbon. The results obtained with catalytic amounts of base are in accord with this pathway for the formation of II. Here the low concentrations of base would be expected to be less favorable for the reversal of the Michael reaction at oxygen. We were, however, unable to repeat the work of Lichtenberg. In our hands, the maximum yield of II obtained in 2 hr was only 15%. After 24 hr, a 35% yield of isomerized product was found. In all of these isomerization experiments, large amounts of 2-naphthol were isolated together with small quantities of ether (I). The isomerization of I was also carried out for 24 hr in isopropyl alcohol to give a 22% yield of II (77% 2-naphthol). The reaction was unsuccessful in diglyme and methanol, 2-naphthol being isolated in yields of 93–99%. The latter two solvents proved to be unsatisfactory for the cyanoethylation of 2-naphthol (see below); so the results are not surprising. On the basis of the results of our isomerization experiments, and other evidence to follow, most of the C-cyanoethylated compound (II) is considered to be formed directly, only a small amount being derived from the isomerization of the ether (I).

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[1] (a) Presented in part at the 1966 Midwest Regional Meeting of the American Chemical Society, Lawrence, Kan. (b) Supported in part by the NSF Nebraska Cooperative College Teacher Development Program.

[2] Abstracted in part from the M.S. Theses, Creighton University, of (a) K. E. D., 1965, (b) M. E. P., 1967.

[3] H. A. Bruson, *Org. Reactions*, **5**, 79.

[4] H. A. Bruson, *ibid.*, **5**, 93.

[5] G. S. Misra and R. S. Asthana, *Ann.*, **609**, 240 (1957).

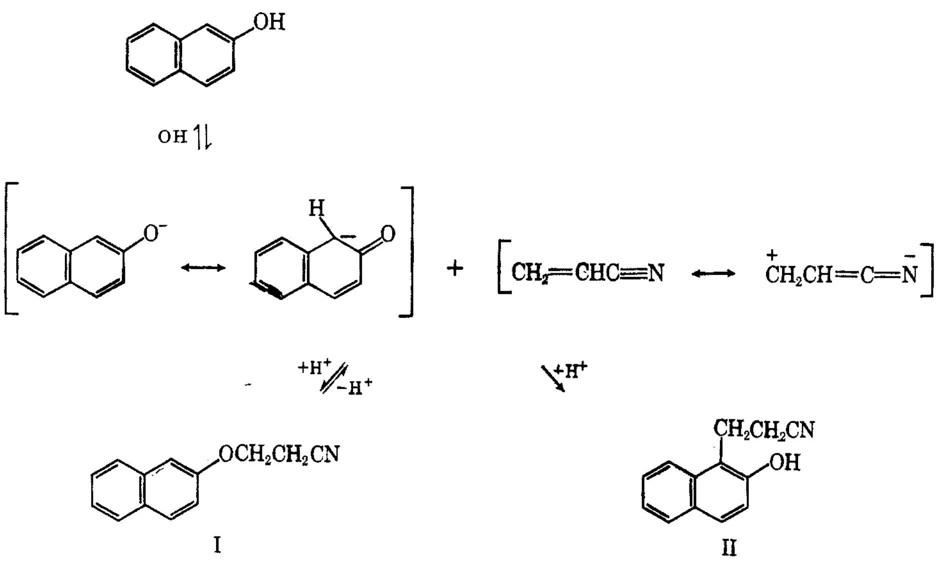
[6] A. F. Hardman, *J. Am. Chem. Soc.*, **70**, 2119 (1948).

[7] G. B. Bachman and H. A. Levine, *ibid.*, **69**, 2343 (1947).

[8] J. Lichtenberg, J. Core, and H. Geyer, *Bull. Soc. Chim. France*, 997 (1962).

[9] (a) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959); (b) N. Kornblum and R. Seltzer, *ibid.*, **83**, 3668 (1961); (c) N. Kornblum, F. J. Berrigan, and W. J. le Noble, *ibid.*, **85**, 1141 (1963); (d) N. Kornblum, R. Seltzer, and R. Haberfield, *ibid.*, **85**, 1148 (1963).

SCHEME I



Kornblum, in his studies of the reaction of 2-naphthoxide ion with benzyl bromide, observed that O alkylation was favored by aprotic solvents of high dielectric constant, whereas C alkylation was favored by aprotic solvents of low dielectric constant and by protic solvents.[9d] In the sodium hydroxide catalyzed reaction of acrylonitrile with 2-naphthol, the solvent was generally found to have little influence on the reaction course (see Table II). The concentration of base appeared to be of greater importance. In all solvents where significant cyanoethylation occurred (benzene, tetrahydrofuran (THF), acetonitrile, acrylonitrile, *t*-butyl alcohol, and isopropyl alcohol), the C-cyanoethylated compound (II) was the predominant, or only, product in the presence of equimolar base. Formation of ether I was favored when catalytic quantities of base were used, except in the protic solvents, isopropyl and *t*-butyl alcohols. The principal product in these solvents was the C-cyanoethylation compound. This is in accord with the observations of Kornblum[9c,d] in his studies of the reaction with alkyl halides that hydrogen bonding solvents inhibit reaction at oxygen. These results give additional support for the extensive formation of II without the intermediacy of I.

TABLE II

CYANOETHYLATION OF 2-NAPHTHOL[a]

Solvent	Dielectric constant[b]	NaOH[c] concn	Yields of products, % I (O)	II (C)
Aprotic				
Benzene	2.3	Cat.	21	4
		Equimolar	0	60
Tetrahydrofuran	7	Cat.	11	1
		Equimolar	0	28
Diglyme	7[d]	Cat.	4	0
		Equimolar	0	1
Acetonitrile	37	Cat.	1	0
		Equimolar	0	36
Dimethylformamide	37	Equimolar	1	0
Acrylonitrile	39	Cat.	41	15
		Equimolar[e]	11	40
Dimethyl sulfoxide	45	Cat.	1	0
		Equimolar	0	0
Protic				
t-Butyl alcohol	10.9	Cat.	3	29
		Equimolar	0	61
Isopropyl alcohol	18	Cat.	2	30
		Equimolar	0	44
Methyl alcohol	33	Equimolar	0	0[f]
Water	80	Equimolar	0	0

[a] Equimolar (*ca.* 0.034 mole) 2-naphthol and acrylonitrile in 50 ml of solvent, bath temperature 95–100°, 24 hr. [b] Bath temperature 20–25°. [c] Cat., *ca.* 0.001 mole in benzene; all other solvents, 0.004–5 moles. [d] Estimated value (ethylene glycol dimethyl ether, 7). [e] Sodium 2-naphthoxide in excess acrylonitrile. [f] Alcohol–nitrile adduct detected in reaction mixture.

The influence of the concentration of sodium hydroxide on the cyanoethylation of 2-naphthol may be accounted for in the following way.[10] Acrylonitrile is susceptible to reversible attack by the nucleophilic naphthoxide ion at either the β carbon or the nitrile-group carbon to give intermediate III or IV, respectively. Naphthol which has not combined with base, present in those reactions with catalytic quantities of base, could conceivably favor the formation of III (Scheme II). Association of the naphthol with the nitrile nitrogen, either as a proton donor or by hydrogen-bond formation would enhance the electrophilic character of the β carbon of acrylonitrile.[11] Attack of this carbon by the electron-rich oxygen of naphthoxide ion yields intermediate III; protonation of III then affords the ether (I). The naphthol as a proton donor would also favor the equilibrium III–I. Degradation of the ether by way of a retro Michael reaction would be inhibited. Some evidence demonstrating this influence of unchanged naphthol is summarized in Table III. The yields of ether were found to be increased by the addition of 2-naphthol to reactions which were found previously to give little or no ether (compare expt 1 and 2 and expt 4 and 5). Experiment 3 shows, however, that even in the presence of excess unchanged naphthol, the ether produced is eventually cleaved on extended heating in the basic medium.

With equimolar quantity of base and 2-naphthol, unaltered naphthol is absent, or present only in relatively

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(10) We wish to thank the referee for suggesting some of the ideas and the experiments to be discussed below.

(11) H. A. Bruson, *Org. Reactions*, **5**, 85. The cyanoethylation of certain amines is facilitated by acidic catalysts.

SCHEME II

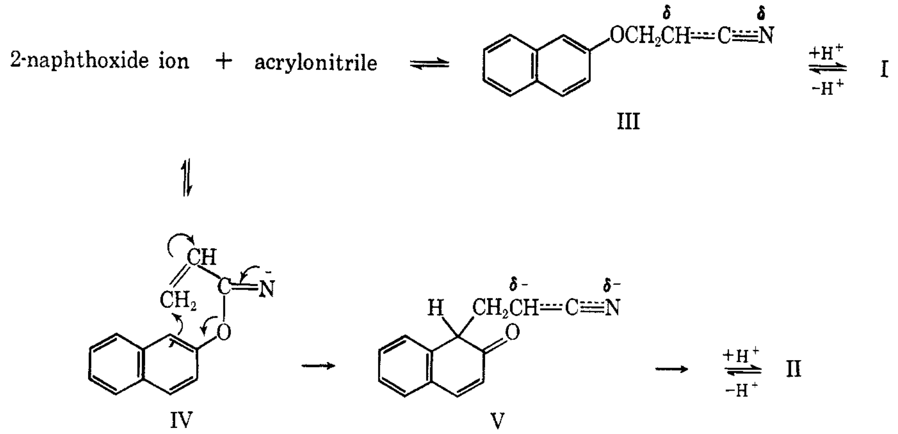

TABLE III
CYANOETHYLATION OF 2-NAPHTHOL AND THE EFFECT OF UNCHANGED NAPHTHOL

Expt	Naphthol added,[a] mole	Solvent	Reaction time, hr	Yields of products, %
1	0	Benzene	2	I, 4 II, 47
2	0.031	Benzene	2	I, 22 II, 43
3	0.031	Benzene	24	I, 1 II, 53
4	0	THF	2	I, 0 II, 2
5	0.031	THF	2	I, 9 II, 1

[a] The standard reaction mixture contains equimolar (0.034 mole) amounts of naphthol, nitrile, and NaOH in 50 ml of solvent.

low concentration. Conditions are less favorable for the equilibrium reactions leading to the formation of ether. The C-cyanoethylated compound (II) is then formed, possibly by way of a six-center reaction, IV–V.[12]

Heterogeneity, or homogeneity, of the reaction mixture was observed to influence the alkylation of phenoxide ions with alkyl halides.[9a] Such does not appear to be the case here. The reactions in benzene, and those with equimolar concentration of base in isopropyl alcohol, *t*-butyl alcohol, and acrylonitrile, were heterogeneous. In others, the reaction was heterogeneous initially owing to the presence of undissolved sodium hydroxide. However, the base completely dissolved within 1–2 hr and the reaction mixture was then homogeneous. The results of the experiments do not show any noticeable effect because of these differences.

Water was an unsatisfactory solvent for the reaction. The reason may be that water can also form an adduct with acrylonitrile.[13] In all of the experiments wherein sodium hydroxide was employed as catalyst, water was produced from the reaction of base with naphthol. The water might be expected to affect these reactions by decreasing the amount of available acrylonitrile. To exclude the presence of this water, preformed sodium 2-naphthoxide was used in several experiments; the yields of cyanoethylated naphthols were not always increased (see Experimental Section). Nonetheless, except for some variations in yields, the results were qualitatively the same whether preformed sodium 2-naphthoxide was used, or the naphthoxide ion was generated in the reaction. Other effects, if any, due to the water were not investigated.

Methyl alcohol was a poor solvent. No cyanoethylation of 2-naphthol was noted in this medium. Alcohols are known to add to acrylonitrile in an equilibrium reaction, the position of which is more favorable for the cyanoethylation product with primary than with secondary alcohols.[14] Tertiary alcohols react slowly or not at all. These facts may account for the poor character of methyl alcohol, and the suitable nature of isopropyl and *t*-butyl alcohols, as solvents for the cyanoethylation of 2-naphthol. Indeed, where methanol was used as solvent, the alcohol–acrylonitrile adduct was detected in the reaction mixture.

Unexpectedly, diglyme, dimethylformamide, and dimethyl sulfoxide were found to be poor solvents for the reaction.[15] No explanation is apparent.

Experimental Section

All melting points were determined using a Fisher-Johns melting point block and are corrected.

The 2-naphthol and sodium hydroxide used were of reagent quality. Purified acrylonitrile (Matheson Coleman and Bell) (bp 75.7–77.5°) was used. Reagent grade benzene and tetrahydrofuran were distilled from sodium. Diglyme was distilled from lithium aluminum hydride. Dimethylformamide and dimethyl sulfoxide were distilled from calcium hydride. All other solvents were of reagent grade and used without further purification.

Authentic samples of β-(2-naphthoxy)propionitrile (I) and 1-(β-cyanoethyl)-2-naphthol (II) were prepared according to published procedures:[6,7] compound I, mp 106–107° (lit.[7] mp 105.5–107°); compound II, mp 141–142° (lit.[6] mp 142°).

Cyanoethylation Experiments.—All reactions were carried out under dry nitrogen in flasks equipped with condenser and magnetic stirrer. The reaction mixtures were heated by means of an oil bath (temperature 95–100°).

A. **Sodium Hydroxide Catalyst.**—In a typical run, 5.0 g (0.034 mole) of 2-naphthol and 1.8 g (0.034 mole) of acrylonitrile in 50 ml of solvent were heated with 0.034 mole (or 0.001–0.005 mole) of sodium hydroxide. In those reactions where the solvent was immiscible with water, after the heating period, the reaction

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[12] The formation of C-cyanoethylated compound is considered to be essentially irreversible. More than 90% of the compound was recovered unchanged on heating for 6 hr with an equimolar quantity of sodium hydroxide in benzene.

[13] H. A. Bruson, *Org. Reactions*, **5**, 89.

[14] H. A. Bruson, *ibid.*, **5**, 90.

[15] Although these solvents were poor for the reaction in this investigation, they may be suitable for other cyanoethylation reactions. For example, the biscyanoethylation of benzyl cyanide was accomplished in diglyme (ref 2b)

mixture was diluted with water. The acidic and neutral materials were separated by the usual extraction procedures. Where the solvent was miscible with water, the reaction mixture was acidified with acetic acid; most of the solvent was then removed under reduced pressure. The residue was processed as described above.

The neutral fraction was chromatographed on alumina (Fisher). Elution with benzene yielded the O-cyanoethylated product (I), mp 104–106°, which was identified by mixture melting point. The acidic material was chromatographed on silica gel (Davison). Unchanged 2-naphthol was eluted with benzene; elution with ether–benzene gave the C-cyanoethylation product (II), mp 140–142°, characterized by mixture melting point. The two cyanoethylation products together with the recovered naphthol accounted for 85–95% of the 2-naphtol employed.[16]

B. Sodium 2-Naphthoxide.—These reactions were carried out as described above in part A except that appropriate quantities of sodium 2-naphthoxide[9d] were substituted for the 2-naphthol and/or base. (1) The equimolar, 24-hr reaction (solvent, yields) showed benzene, 0% I, 70% II; tetrahydrofuran, 1% I, 20% II; acetonitrile, 0% I, 23% II; *t*-butyl alcohol, 0% I, 50% II; water, 0% I, 0% II; (2) catalytic, 24-hr reaction, benzene, 17% I, 5% II; *t*-butyl alcohol, 4% I, 33% II; and, (3) equimolar with added naphthol, 2-hr reaction, benzene, 19% I, 52% II.

Isomerization of β-(2-Naphthoxy)propionitrile (I).[8]—A mixture of 5.0 g (0.025 mole) of the β-cyanoethyl ether (I) and 1.0 g (0.025 mole) of sodium hydroxide in 50 ml of benzene was refluxed for 2 hr under nitrogen. The heterogeneous reaction mixture was diluted with water, and separated into neutral and acidic fractions. Chromatography of the fractions as described above gave the following yields: unchanged I, 10%; II, 4%; 2-naphthol, 84%. The reaction was repeated several times: maximum yield of II, 15%. The reaction time was extended to 24 hr: yield of unchanged I, 5%; II, 35%; 2-naphthol, 54% (average of two runs).

The reaction was also repeated for 24 hr in isopropyl alcohol (yields II, 22%; 2-naphthol, 77%), diglyme (99% naphthol), and methanol (93% naphthol).

Registry No.—I, 14233-72-8; II, 14233-73-9; 2-naphthol, 135-19-3.

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[16] Evidence for the formation of any significant amounts of biscyanoethylated naphthol was absent.

The Controlled Synthesis of Peptides in Aqueous Medium. III. Use of Leuchs' Anhydrides in the Synthesis of Dipeptides. Mechanism and Control of Side Reactions[1]

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Received April 27, 1967

The successful use of N-carboxy-α-amino acid anhydrides (NCA's) in the controlled synthesis of optically pure dipeptides in aqueous medium is described. High yields of dipeptides were obtained by adding the crystalline NCA directly to an aqueous solution of an amino acid at 0–2° and generally at pH 10.2 with rapid mixing of reactants, thus minimizing side reactions. In the case of relatively insoluble NCA's, rapid mixing enhances the rate of dissolution of the NCA and thereby reduces the opportunity for carbamate exchange, which leads to overreaction (formation of tripeptide) and to inactivation of the starting amino acid. With the more soluble NCA of alanine, rapid mixing was shown to reduce greatly the amount of overreaction brought about by oligomerization of the NCA *via* its anion. The control of pH is important because carbamate stability increases with pH, but at a pH above 10.5 hydrolysis of the NCA becomes an important side reaction and the formation of the NCA anion is increased. This anion is believed to be responsible for the formation of hydantoic acids, a side reaction not previously observed under these conditions. Low temperature favors the desired reaction over side reactions partly because of the change in K_w with temperature. With careful control of reaction conditions, the NCA method permits the rapid synthesis of optically pure peptides with the use of a minimum number of protecting groups. Dipeptides are generally formed in about 90% yield. Examples are given for the isolation of the dipeptides by a variety of methods. ^{14}C-Labeled amino acids were frequently employed for the radiochemical analysis of reaction mixtures.

N-Carboxy-α-amino acid anhydrides (Leuchs' anhydrides, NCA's) have been used widely[2] in polymerization reactions in anhydrous media for the synthesis of homopeptides and the random synthesis of heteropeptides. On the other hand, NCA's have been reported not to possess general utility in the controlled synthesis of heteropeptides.[3,4] About 40 years ago, Wessely described the use of N-carboxy-N-phenylglycine anhydride in the preparation of N-phenylglycylglycine and of N-phenylglycyl-L-tyrosine ethyl ester.[5a] One year later,[5b] the condensation of N-carboxy-DL-phenylalanine anhydride with glycine and with glycylglycine was reported. More recently this NCA was used in the synthesis of phenylalanylphenylalanine.[6] In these experiments the NCA was dissolved in a water-immiscible solvent and allowed to react with an aqueous solution of the amino acid or peptide. In 1957, Bartlett and his collaborators,[7,8] investigating the potential of the method, undertook a study of the reactions of the NCA's of glycine, alanine, α-aminoisobutyric acid, and phenylalanine with aqueous solutions of amino acids, glycylglycine, and triglycine. They concluded that the reaction cannot be controlled adequately to provide a useful general method for peptide synthesis in water.

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[1] (a) A preliminary report dealing with certain aspects of this work has appeared: R. G. Denkewalter, H. Schwam, R. G. Strachan, T. E. Beesley, D. F. Veber, E. F. Schoenewaldt, H. Barkemeyer, W. J. Paleveda, Jr., T. A. Jacob, and R. Hirschmann, *J. Am. Chem. Soc.*, **88**, 3163 (1966); (b) E. F. Schoenewaldt, R. G. Denkewalter, H. Joshua, R. G. Strachan, H. Schwam, D. F. Veber, W. J. Paleveda, Jr., and R. Hirschmann, presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

[2] For recent reviews, see V. V. Korshak, S. V. Rogozhin, V. A. Davankov, Yu A. Davidovich, and T. A. Makarova, *Russ. Chem. Rev.*, 329 (1965). M. Szwarc, *Advan. Polymer Sci.*, **4**, 1 (1965).

[3] M. Brenner and W. Hofer, *Helv. Chim. Acta*, **44**, 1798 (1961).

[4] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1961, p 860, and M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, Inc., New York, N. Y., 1966, provide recent reviews.

[5] (a) F. Wessely, *Z. Physiol. Chem.*, **146**, 72 (1925); (b) F. Sigmund and F. Wesseley, *ibid.*, **147**, 91 (1926).

[6] F. Wessely, K. Schogl, and G. Korger, *Monatsh. Chem.*, **82**, 672 (1951).

[7] P. D. Bartlett and R. H. Jones, *J. Am. Chem. Soc.*, **79**, 2153 (1957).

[8] P. D. Bartlett and D. C. Dittmer, *ibid.*, **79**, 2159 (1957).