[Contribution from the Research Laboratories, Phosphate Division, Monsanto Chemical Company]

# Phosgene Derivatives. The Preparation of Isocyanates, Carbamyl Chlorides and Cyanuric Acid[1]

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At the time the major portion of this work had been completed the vapor phase reaction between phosgene and amines had not been described.[2] However, a somewhat similar reaction was reported recently.[3] The use of catalysts, preheating of the phosgene, and relatively long sojourn times (2.3–17.7 sec.) were recommended. Work reported here more closely defines the conditions of the reaction and shows that the recommendations cited above are not necessary.

This process has been made the basis of a general synthetic procedure for the preparation of carbamyl chlorides and isocyanates.

The development of this procedure was prompted by a study of the preparation of methylcarbamyl chloride by passing phosgene over molten methylamine hydrochloride.[4,5] Experiments showed that the yield of isocyanate was adversely affected when the area of contact was increased by dispersing phosgene beneath the surface of the molten salt. This observation suggested that the reaction involved not only the liquid–gas interfacial contact, but also depended upon conditions in the gas phase. It was reasoned that some of the methylamine hydrochloride was vaporized and dissociated and that the free amine may then have reacted with phosgene. If this were true, a direct reaction between methylamine and phosgene in the vapor-phase should be feasible. Such a reaction was carried out successfully, and methylcarbamyl chloride was obtained, which was converted by more orthodox methods to the isocyanate in 88% over-all yield.

The vapor-phase method for the preparation of methyl isocyanate was found to have wide applicability. A variety of mono- and disubstituted carbamyl chlorides and isocyanates were prepared in 70 to 90% yield by the reaction between phosgene and primary or secondary amines at 275°.

$$RNH_2 + COCl_2 \longrightarrow RNHCOCl + HCl$$

$$RNHCOCl \rightleftarrows RNCO + HCl$$

$$R_2NH + COCl_2 \longrightarrow R_2NCOCl + HCl$$

The isocyanate was obtained from the monosubstituted carbamyl chloride by treatment with a tertiary amine. Those isocyanates which boil above 120° were also liberated by refluxing the corresponding monosubstituted carbamyl chloride in benzene or toluene.

The method is applicable apparently to the use of any primary or secondary monoamine which can be boiled readily without decomposition. For practical purposes the procedure is limited to amines containing from one to twelve carbon atoms. Only two conditions were found necessary for the satisfactory operation of the vapor-phase reaction. These were, (1) the amine vapor must be adequately mixed with phosgene, and (2) the reaction zone must be hot enough to avoid the separation of reaction products from the gas phase in that zone.

Similarly, at 500° ammonia was converted to carbamyl chloride in almost quantitative yield.

$$NH_3 + COCl_2 \longrightarrow H_2NCOCl + HCl$$

The reaction between ammonia and phosgene at 400° was mentioned by Rupe and Labhard,[6] but no experimental details were given. When this reaction was run at 400°, considerable amounts of ammonium chloride were formed. In contrast, at 500° this undesirable by-product was almost entirely eliminated. The carbamyl chloride was readily converted to cyanuric acid by heating to 180°

$$3H_2NCOCl \longrightarrow (HNCO)_3 + 3HCl$$

A consideration of the temperatures used in the vapor-phase reaction and in the thermal decomposition of monosubstituted carbamyl chlorides[4,5] indicates that the isocyanate is the end-product of the vapor-phase reaction at 275° when primary amines are employed, but, upon cooling, the isocyanate may combine with hydrogen chloride to give the carbamyl chloride.

That this sequence is true was demonstrated by removing the hydrogen chloride from the products of the reaction before combination with the isocyanate could occur. As typical examples, methyl, phenyl and octyl isocyanates were prepared directly without the intermediate formation of the carbamyl chlorides.

## Experimental

**General Method for the Preparation of Carbamyl Chlorides.**—The apparatus is shown in Fig. 1. The reactor (K) was made of 15-mm. i. d. Pyrex tubing. The heated portion was 15 in. long and wound with $^1/_{16}$-in. nichrome ribbon having a resistance of 15 ohms. Phosgene entered the reaction zone (M) through a 6-mm. tube (A) which was drawn out to a 1-mm. tip. Amine vapor entered the reaction zone through the annular space between the phosgene inlet tube and the reactor tube. Indentations were made in the walls of the reactor to impart added turbulence to the gases.

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[1] The work described in this paper was done in part under Contract OEM-sr-845, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development, and the Monsanto Chemical Company. A portion of this work has been described by Jenkins and Hardy in Off. Pub. Bd. Report, P. B. 27396, "The Preparation of Isocyanates, Cyanuric Acid, and Decontaminant 40."

[2] Saunders and Slocombe, *Chem. Revs.*, **43**, 203 (1948).

[3] Modersohn, "Action of Phosgene on Primary and Secondary Amines in the Gas Phase," Off. Pub. Bd., Report PB 707.

[4] Gattermann and Schmidt, *Ber.*, **20**, 118 (1887).

[5] Gattermann, *Ann.*, **244**, 29 (1888).

[6] Rupe and Labhard, *Ber.*, **33**, 233 (1900).

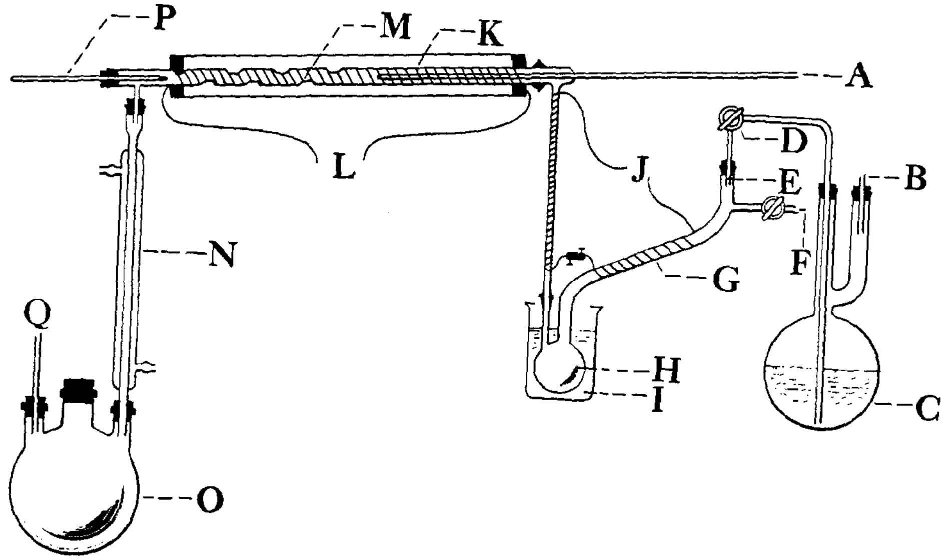

Fig. 1.—Vapor-phase reaction apparatus: A, phosgene inlet from flowmeter; B, nitrogen inlet to amine feed flask; C, amine feed flask; D, amine flow control cock; E, calibrated tip for amine addition; F, nitrogen inlet for sweeping; G, preheater section of vaporizer; H, flash vaporizer; I, salt-bath heated with bunsen burner; J, electrical leads to vaporizer heaters; K, reactor tube; L, electrical leads to reactor heater; M, reaction zone; N, product condenser; O, receiving flask; P, thermometer for reactor outlet temperature; Q, off-gas outlet.

The salt-bath (I) for the flash vaporizer (H) was heated to a temperature at least 100° above the boiling point of the amine being used. A weighed amount of the desired amine, if a liquid at room temperature, was charged into the amine feed flask (C). Nitrogen pressure ($^1/_2$ to $^1/_4$ p. s. i. from a cylinder reducing valve) was applied to the amine feed flask at (B) to force the liquid to the stopcock (D) which controlled the rate of amine flow. If the amine was a gas at room temperature it was fed from a cylinder through an orifice-type flow meter. In such cases the amine vaporizer was not used.

The reactor (K) was heated to a temperature of 275°, read at (P), while a slow stream of nitrogen was sweeping through the system from the nitrogen inlet (F) on the side of the amine preheater (G). The phosgene was turned on to the desired rate as shown by an orifice-type flowmeter. The amine addition was then begun. The maximum rate of addition of liquid amine was estimated from the rate of drop formation at (E). A phosgene:amine molar ratio of 1.3 was used. The flow of nitrogen was used only when the operation was started, interrupted or terminated. The nitrogen served to prevent phosgene or hydrogen chloride from backing into the amine vaporizing system and forming a deposit of the urea and the amine hydrochloride. Excess phosgene was decomposed with steam.

The limits of the conditions for the reaction are broad. Reaction temperatures of 240–350°, sojourn times of 0.24–2.6 sec., and phosgene–amine molar ratios as low as 1.2 have been used with good success.

## Conversion of Carbamyl Chlorides to Isocyanates

**(a) Use of a Tertiary Amine.**—Into a 1-l., 3-necked flask was placed 150 g. of crude methylcarbamyl chloride obtained from 49 g. (1.57 moles) of methylamine. The flask was fitted with a reflux condenser, mechanical stirrer and dropping funnel. A solution of 165 ml. (2.0 moles) of dry pyridine and 165 ml. of dry toluene was added slowly with stirring. Vigorous reaction accompanied this addition. The resulting solution was distilled through an 18-in., helix-packed column. The yield of methyl isocyanate, b. p. 37–39°, was 79 g., 88% based on amine.

Other isocyanates below amyl were obtained by adding dimethylaniline directly to the carbamyl chloride and distilling. One-fourth molar excess of amine was used. Yields and physical properties are given in Table I.

In spite of extreme care to avoid the presence of moisture, crystals frequently occurred in *n*-butyl and *s*-butyl isocyanates when these isocyanates were distilled at atmospheric pressure. Distillation at 20 mm. gave crystal-free products.

*n*-Butyl isocyanate showed a marked tendency to polymerize in the presence of the tertiary amine hydrochloride. An equal volume of "orthene" (technical *o*-dichlorobenzene) and of dimethylaniline were used to decompose the butylcarbamyl chloride. The final reaction mixture was cooled to freeze out the amine hydrochloride. The supernatant liquid was decanted and distilled with good yields.

**(b) Refluxing with an Inert Solvent.**—The crude phenylcarbamyl chloride obtained from 50 g. of aniline was dissolved in 75 ml. of toluene or benzene and refluxed until no more hydrogen chloride was evolved. On fractional distillation, 55 g. (86%) of phenyl isocyanate was collected, b. p. 158–162°. Other carbamyl chlorides above butyl were converted to the isocyanate by this method. Yields and physical data are given in Table I.

**Disubstituted Carbamyl Chloride.**—The general procedure was the same as for the monosubstituted carbamyl chlorides. The reaction product was refluxed with one-half its weight of dry toluene to drive out dissolved phosgene and hydrogen chloride. The solvent was removed and the product distilled. Yields and physical data are given in Table I.

**Carbamyl Chloride.**—The general procedure was the same as that used in the preparation of substituted carbamyl chlorides, with the following exceptions. In the first experiments carbamyl chloride was collected as a colorless liquid. In later experiments the receiver equipped with a reflux condenser and a mechanical stirrer, and containing 1.5 to 2.0 l. of orthene, was attached directly to the vapor-phase reactor. The reaction temperature was 500°.

The undiluted carbamyl chloride showed a marked tendency to solidify below room temperature, and to lose hydrogen chloride and polymerize on standing. When the carbamyl chloride was to be used at once in the synthesis of cyanuric acid, orthene was put in the receiver and stirred to prevent caking of the solid. No yield of pure carbamyl chloride was determined.

TABLE I

PREPARATION OF ISOCYANATES AND DISUBSTITUTED CARBAMYL CHLORIDES

| Amine | Boiling range of product, °C. (uncor.) | Yield, % |
|---|---|---|
| Methyl | 37–39[4,5] | 88 |
| Ethyl | 58–61[a] | 71 |
| *n*-Propyl | 86–88[b] | 76 |
| Isopropyl | 70–75[c] | 82 |
| Allyl | 83–85[d] | 75 |
| *n*-Butyl | 113–116[e,f] | 70 |
| *s*-Butyl | 99–101[g] | 70 |
| Isobutyl | 100–103[h] | 78 |
| Amyl (mixed) | 129–140[i] | 70 |
| Cyclohexyl | 165–168[j] | 88 |
| Phenyl | 158–162[k] | 86 |
| *n*-Octyl | 200–204[l] | 81 |
| *n*-Dodecyl | 130–140 (4 mm.)[f] | 58 |
| Dimethyl | 166–168[m] | 90 |
| Di-*n*-butyl | 245–247[n] | 81 |
| Diamyl (mixed) | 115–125 (3 mm.)[o] | 83 |

[a] Wurtz, *Ann. chim. phys.*, [3] **42**, 43 (1854); $n^{20}_{\mathrm{D}}$ 1.3801; $d^{20}_{4}$ 0.9039.[7] [b] Oliveri-Mandalà and Noto, *Gazz. chim. ital.*, **43**, I, 514 (1913). [c] Hofmann, *Ber.*, **15**, 752 (1882); $n^{20}_{\mathrm{D}}$ 1.3886; $d^{20}_{4}$ 0.8669.[7] [d] Hofmann, *Ann.*, **102**, 285 (1857). [e] *Anal.*[7] Calcd.: C, 60.58; H, 9.15. Found: C, 60.42; H, 8.84; $n^{20}_{\mathrm{D}}$ 1.4060; $d^{20}_{4}$ 0.880. [f] U. S. Patent 2,326,501. [g] *Anal.*[7] Calcd.: C, 60.58; H, 9.15. Found: C, 60.80; H, 9.02; $n^{20}_{\mathrm{D}}$ 1.3989; $d^{21}_{4}$ 0.8804. [h] Anschutz, *Ann.*, **359**, 202 (1908). [i] Sharples mixed amylamines were used: Custer, *Ber.*, **12**, 1328 (1879). [j] Skita and Rolfes, *ibid.*, **53**, 1242 (1920). [k] Hofmann, *ibid.*, **3**, 653 (1870). [l] *Anal.*[7] Calcd.: C, 69.63; H, 11.04. Found: C, 70.14; H, 11.25; $n^{20}_{\mathrm{D}}$ 1.4314; $d^{20}_{4}$ 0.8768. [m] Michler and Escherich, *Ber.*, **12**, 1162 (1879). [n] Werner, *J. Chem. Soc.*, **115**, 1010 (1919). [o] Sharples mixed diamylamines were used: Atkinson, *J. Chem. Soc.*, **105**, 1290 (1914).

**Cyanuric Acid.**—The crude carbamyl chloride was converted to cyanuric acid[8] by heating at about 180° for three hours. The temperature rose slowly from 55 to 180°, as hydrogen chloride was evolved and polymerization progressed. When no solvent was used the cyanuric acid could not be recovered without breaking the flask. When orthene was used as a solvent the product was readily obtained by filtering the resulting slurry and drying the finely divided solid at 200–210°. The yield was 82–89%, based on ammonia. The cyanuric acid, without further processing, was 98% pure, as indicated by a Kjeldahl analysis and solubility in alkali. The isomeric cyamelid is insoluble in dilute alkali.[9]

*Anal.*[10] Calcd. for $C_3H_3O_3N_3$: N, 32.56. Found: N, 31.9, 31.9.

**Solubility of Hydrogen Chloride in Phenyl Isocyanate.**—In order to demonstrate the lowest temperature at which phenyl isocyanate can be condensed from the reaction gases without the formation of phenylcarbamyl chloride, the stability of phenylcarbamyl chloride was observed briefly.

(a) **Toluene Solution.**—A 1-l., 3-necked flask was fitted with a sealed mechanical stirrer, a gas inlet tube, a thermometer, and a condenser, which in turn was connected to a trap cooled in a Dry Ice–methanol-bath. A solution of 100 g. (0.84 mole) of phenyl isocyanate in 500 ml. of dry toluene was placed in the flask. The toluene solution was maintained at 50°. Dry hydrogen chloride was bubbled into the solution until a constant weight was reached. Correction was made for any toluene or isocyanate which was condensed in the cold trap. The gain in weight of the solution was taken as the weight of hydrogen chloride absorbed. The process was repeated at 80, 95 and 105°. The data are recorded in Table II.

TABLE II

ABSORPTION OF HYDROGEN CHLORIDE BY 100 G. OF PHENYL ISOCYANATE

| Temp., °C. | No solvent HCl, g. | No solvent RNHCOCl, % | In 500 ml. toluene HCl, g. | In 500 ml. toluene RNHCOCl. % |
|---|---|---|---|---|
| 50 | ........ | ........ | 32.3 ± 0.9 | 100 |
| 80 | ........ | ........ | 11.7 ± 0.5 | 38.2 ± 2 |
| 95 | 11.2 ± 0.1 | 36.6 ± 0.5 | 4.5 ± 0.6 | 14.7 ± 2 |
| 105 | 6.7 ± 0.1 | 21.9 ± 0.2 | 1.7 ± 0.3 | 5.6 ± 1 |
| 115 | 4.0 ± 0.1 | 13.2 ± 0.3 | ........ | ........ |
| 125 | 1.9 ± 0.1 | 6.1 ± 0.4 | ........ | ........ |

It is apparent that condensation of phenyl isocyanate in boiling toluene will not be accompanied by the formation of appreciable amounts of phenylcarbamyl chloride.

(b) **No Solvent.**—The procedure described for the determination in toluene solution was followed, except that no solvent was used. The absorption of hydrogen chloride was observed at 95, 105, 115 and 125°. The weight of hydrogen chloride absorbed was determined by titration of the chloride in the isocyanate–carbamyl chloride solution.[10] The data are recorded in Table II. These results are in general agreement with those of Lengfeld and Stieglitz, who reported that phenylcarbamyl chloride dissociates at 100°.[11]

**The Direct Preparation of Phenyl Isocyanate.**—The procedure for the reaction between phosgene and aniline was the same as that used for carbamyl chlorides, with the following changes. The gaseous products passed from the reactor into a 20-mm. Pyrex tube which was heated electrically to 130°. This tube extended almost to the bottom of a 500-ml., 3-necked flask which contained 250 ml. of refluxing toluene. To the flask was attached an 8-in. bead-packed column, which was heated externally to maintain a temperature of 110° inside the column. A long condenser was placed on top of the column. From 50 g. (0.54 mole) of aniline there was obtained 52.3–56.8 g. (82–89%) of phenyl isocyanate, b. p. 157–162°.

Analysis of the crude reaction mixture before distillation indicated the presence of only traces of chloride.

**The Direct Preparation of *n*-Octyl Isocyanate.**—The apparatus and procedure were the same as the preceding description for phenyl isocyanate. From 320 g. (2.48 moles) of *n*-octylamine there was obtained 339 g. (88%) of *n*-octyl isocyanate, b. p. 200–207°.

**The Direct Preparation of Methyl Isocyanate.**—The reactor and method described for carbamyl chlorides were used, with the following modifications. A 20-mm. Pyrex tube led from the reactor to a 3-l. flask which contained 450 g. of dry pyridine and 250 ml. of dry toluene. The connecting tube extended to within 1 in. of the surface of the liquid in the flask, and was heated electrically to 140°. An 8-in. Vigreux column was attached to one neck of the flask. On top of this column was placed an 8-in. helix-packed column, partial take-off head, and condenser, which was connected to a Dry Ice–methanol trap. The pyridine–toluene mixture was boiled vigorously. During the reaction distillate boiling at 60–80° was collected from the partial take-off head. When the reaction was completed the distillation was continued until the distillate boiled at 112°. Redistillation of this crude product gave methyl isocyanate, b. p. 37–41°. From 36 g. (1.16 moles) of methylamine there was obtained 40 g. of methyl isocyanate, 60.7%, based on amine. Essentially no methylcarbamyl chloride was formed, since the pyridine combined

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(7) We are indebted to the Clark Microanalytical Laboratory, Urbana, Illinois, for the analytical determinations.

(8) Rupe and Metz, *Ber.*, **36**, 1092 (1903).

(9) Hantzsch, Hofmann and Lehmann, *ibid.*, **38**, 1013 (1905).

(10) The authors wish to thank Mr. W. B. Dunlap for this analysis.

(11) Lengfeld and Stieglitz, *Am. Chem. J.*, **16**, 71 (1894).

with the hydrogen chloride at a temperature above that at which methylcarbamyl chloride dissociates (93–94°).[5]

## Summary

1. The vapor-phase reactions of primary and secondary monoamines with an excess of phosgene were investigated. A new method for the preparation of mono- and disubstituted carbamyl chlorides and of monoisocyanates from aliphatic, olefinic, alicyclic and aromatic amines is described.

2. Carbamyl chloride was prepared by the reaction between phosgene and ammonia at 500°. The carbamyl chloride was of high purity and was readily converted to cyanuric acid by heating.

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[12] Original manuscript received September 24, 1948.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. LOUIS UNIVERSITY]

# Polarographic, Potentiometric and Conductometric Studies on the Aspartate and Alaninate Complexes of Copper

BY NORMAN C. LI AND EDWARD DOODY[1]

As a part of a general program on complex formation between different metallic and amino acid ions[2] this paper[3] presents the results on the aspartate and alaninate complex of copper. The methods used were polarographic, potentiometric and conductometric.

Several investigators have studied the complex ions formed between cupric and alaninate ions. Boorsook and Thimann[4] have deduced from spectrophotometric and electrometric data that the complex formed in alkaline solutions was $CuA_3^-$. Riley and co-workers[5,6] using a cupric ion concentration cell, have concluded that a very stable complex ion of the type $CuA_3^-$ is formed; however, the data for alaninate solutions reported in the two papers do not agree. Using the dropping mercury electrode, Keefer[7] has reported the composition and stability of the alaninate complex of copper and has found the complex to be $CuA_2$, but it is desirable to extend the range of his studies to lower $p$H values by using buffer solutions.

## Experimental

Reagent quality chemicals were used without further purification except for the alanine which was once recrystallized. A standard solution of cupric nitrate was prepared by dissolving about 0.025 mole of cupric nitrate in 250 ml. of water. To this solution excess potassium iodide was added and the liberated iodine was titrated with a standard solution of sodium thiosulfate to the starch endpoint. Stock solutions of the potassium aspartate and potassium alaninate were prepared from the amino acids and potassium hydroxide and kept in a refrigerator until used. The $p$H of all solutions for the polarographic studies was measured by means of a Leeds and Northrup $p$H meter, assembly number 7661. To minimize errors in calculating the aspartate concentration from the $p$H, the $pK_2$ and $pK_3$ for aspartic acid was determined at the same ionic strength using carbonate-free sodium hydroxide. A simple method for determining the $pK_2$ and $pK_3$ of aspartic acid and equation for calculating the concentration of the aspartate ion will be given later in the paper. For alanine Keefer's value[7] of 9.86 for $pK_2$ was used.

Polarographic measurements were made using a Fisher Elecdropode. An H-type cell was used, with a saturated calomel electrode, in a thermostat kept at 25.0°. Oxygen was removed from the solutions in the cell with a stream of hydrogen and during each run an inert atmosphere of hydrogen was maintained over the solution. Methyl red (0.025%) and brom cresol green (0.12%) were used as a maximum suppressor. In the case of the aspartate, all solutions were made up to $5 \times 10^{-4}$ $M$ cupric nitrate and sufficient potassium nitrate was added to keep the ionic strength constant at 1.0. In the case of alanine, the composition of the solutions was as follows: 0.04 $M$ potassium alaninate, $5 \times 10^{-4}$ $M$ cupric nitrate, 0.06 $M$ potassium dihydrogen phosphate plus sodium hydroxide. The reversibility of the electrode reaction was tested for each analysis by determining the slopes of plots of log $i/(i_d - i)$ against $E_{d.e.}$, or by determining the values of $(E_{3/4} - E_{1/4})$,[8] where $E_{3/4}$ and $E_{1/4}$ are the values of $E_{d.e.}$ at $i = (3/4)i_d$ and $i = (1/4)i_d$, respectively. Corrections were made for residual current. Half-wave potentials were reproducible to ±3 mv.

Potentiometric studies were made using a Cenco Titration-$p$H meter, with a glass electrode which had been cleaned thoroughly with dilute acid, allowed to stand in distilled water for a number of hours, and then calibrated immediately before use by means of a potassium acid phthalate buf-

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[1] Brother Edward Doody of the Congregation of Christian Brothers.

[2] Li and Gormley, a paper presented at the Chicago meeting of the American Chemical Society, April 20, 1948.

[3] Presented at the 116th meeting of the American Chemical Society, Atlantic City, Sept., 1949.

[4] Boorsook and Thimann, *J. Biol. Chem.*, **98**, 671 (1932).

[5] Riley and Gallafent, *J. Chem. Soc.*, 2029 (1931).

[6] Ferrel, Ridgion and Riley, *ibid.*, 1440 (1934).

[7] Keefer, THIS JOURNAL, **68**, 2329 (1946).

[8] Kolthoff and Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.