J. T. Baker Chemical Co., and cesium and rubidium fluorides from American Potash and Chemical Corp. The benzaldehyde, cyclohexanone, and nitromethane were distilled before use. Absolute ethanol, dry benzene, and dimethylformamide were used as solvents.

Condensation of Benzaldehyde and Cyclohexanone with Active Methylene Compounds.—In a typical reaction, 0.1 mole of the carbonyl compound, 0.1 mole of the active methylene, 0.025 mole of potassium fluoride, and 50 ml. of solvent were mixed and maintained at 25 or 60° during the course of the reaction. The reaction mixture was then poured into cold water and extracted with ether. The ether was removed under reduced pressure, and the product was recrystallized from ethanol or distilled. The products obtained were ethyl benzylidenecyanoacetate, m.p. 49–51° (lit.,[3a] m.p. 50–51°) benzylidenemalononitrile, m.p. 83–84° (lit.,[10] m.p. 83.5–84°), cyclohexylidenemalononitrile, b.p. 138–140°/10 mm., n^{25}_{D} 1.5104 (lit.,[11] b.p. 137–138°/10 mm., n^{25}_{D} 1.5110), and ethyl cyclohexylidenecyanoacetate, b.p. 159–165°/15 mm., n^{25}_{D} 1.4963 (lit.,[12] b.p. 150–151°/9 mm., n^{25}_{D} 1.4950). The per cent yields of products isolated are listed in Tables I and II. Those reactions that were analyzed by vapor phase chromatography contained 0.19 mole of the carbonyl compound, 0.19 mole of the active methylene, 0.095 mole of potassium fluoride, 10 ml. of solvent, and the internal standard, tetralin or toluene. The components of the reaction mixture were separated on a 6-ft. "Tide" column, using a Barber-Colman chromatograph, Model 23C. Amounts of starting materials remaining were determined at 0, 6, and 24 hr.

Effect of Catalyst Concentration.—In order to determine if the amount of catalyst had any effect on the results of these condensation reactions, the reaction of 10.6 g. (0.1 mole) of benzaldehyde and 11.3 g. (0.1 mole) or ethyl cyanoacetate in 50 ml. of ethanol was catalyzed by 0.025 mole, 0.050 mole, and 0.1 mole of potassium fluoride, respectively. An essentially quantitative yield of the ethyl benzylidenecyanoacetate was obtained from each reaction after 6 hr. at 60°. When potassium fluoride was omitted, no product could be isolated.

Comparison of Alkali Fluoride Catalysts.—Lithium fluoride, sodium fluoride, potassium fluoride, rubidium fluoride, and cesium fluoride in amounts of 0.0024 mole, were each used to catalyze the reaction between 0.93 g. (0.0095 mole) of cyclohexanone and 1.08 g. (0.0095 mole) of ethyl cyanoacetate in 10 ml. of ethanol at 60°. Tetralin (0.93 g.) was used as an internal standard. The decrease in the concentration of the starting materials was determined by vapor phase chromatography. The results after 90-min. reaction time are shown in Table III.

This reaction was repeated using ten times the quantities of all materials except the catalyst. In the two runs 0.01 g. (0.0024 mole) of sodium fluoride and 0.025 g. (0.0024 mole) of rubidium fluoride were employed. These amounts of catalysts were completely dissolved. The results, determined as above, showed that after 72 hr. the reaction catalyzed by rubidium fluoride had progressed about four times as much as the one catalyzed by sodium fluoride or to about 40% completion.

Solubility of Alkali Fluorides in Ethanol.—The solubilities were determined by adding absolute alcohol from a buret to samples of lithium fluoride (0.25 g.) sodium fluoride (0.50 g.) potassium fluoride (1.00 g.), rubidium fluoride (5.00 g.), and cesium fluoride (10.00 g.) at 27° until solution was complete. The final additions of alcohol were made over several hours and the mixtures were stirred rapidly to hasten solution. The results are summarized in Table IV.

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[10] B. B. Corson and R. W. Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928).

[11] A. C. Cope and K. E. Hoyle, *ibid.*, **63**, 733 (1941).

[12] A. C. Cope, *ibid.*, **59**, 2327 (1937).

Pyrimidines. II. Chlorinated Pyrimidines Derived from Orotic Acid

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The preparation of 2,6-dichloro-4-pyrimidinecarboxylic acid, 2,5,6-trichloro-4-pyrimidinecarboxylic acid, their methyl esters, and intermediates is described. It was also found that the chlorine atoms in the 2- and 6-positions could undergo solvolysis in the presence of methyl alcohol to yield hydroxyl groups, hydrolysis of 2,6-dichloropyrimidine-4-carboxylic acid in boiling water produced uracil instead of the expected orotic acid, and treatment of 5-chloroörotic acid with phosphorus oxychloride and phosphorus pentachloride followed by reduced pressure distillation produced 2,4,5,6-tetrachloropyrimidine.

In the course of our studies on chlorinated pyrimidines, it became desirable to prepare both 2,6-di- and 2,5,6-trichloro-4-pyrimidinecarboxylic acids.

At the time that this program was initiated, the literature[1b,2] on 2,6-dichloro-4-pyrimidinecarboxylic acid was questionable. Recently, Daves,[3] *et al.*, reported the correct structure of the compound and also attempted to explain the results reported earlier.[1,2]

Scheme I summarizes the reaction sequences that were undertaken and the results that were observed, which in a number of cases, were unexpected.

Starting with orotic acid[4] (I), orotyl chloride (II) was produced by refluxing with excess thionyl chloride in the presence of a catalytic quantity of pyridine. Without isolating the acid chloride, methyl alcohol was added both to decompose any

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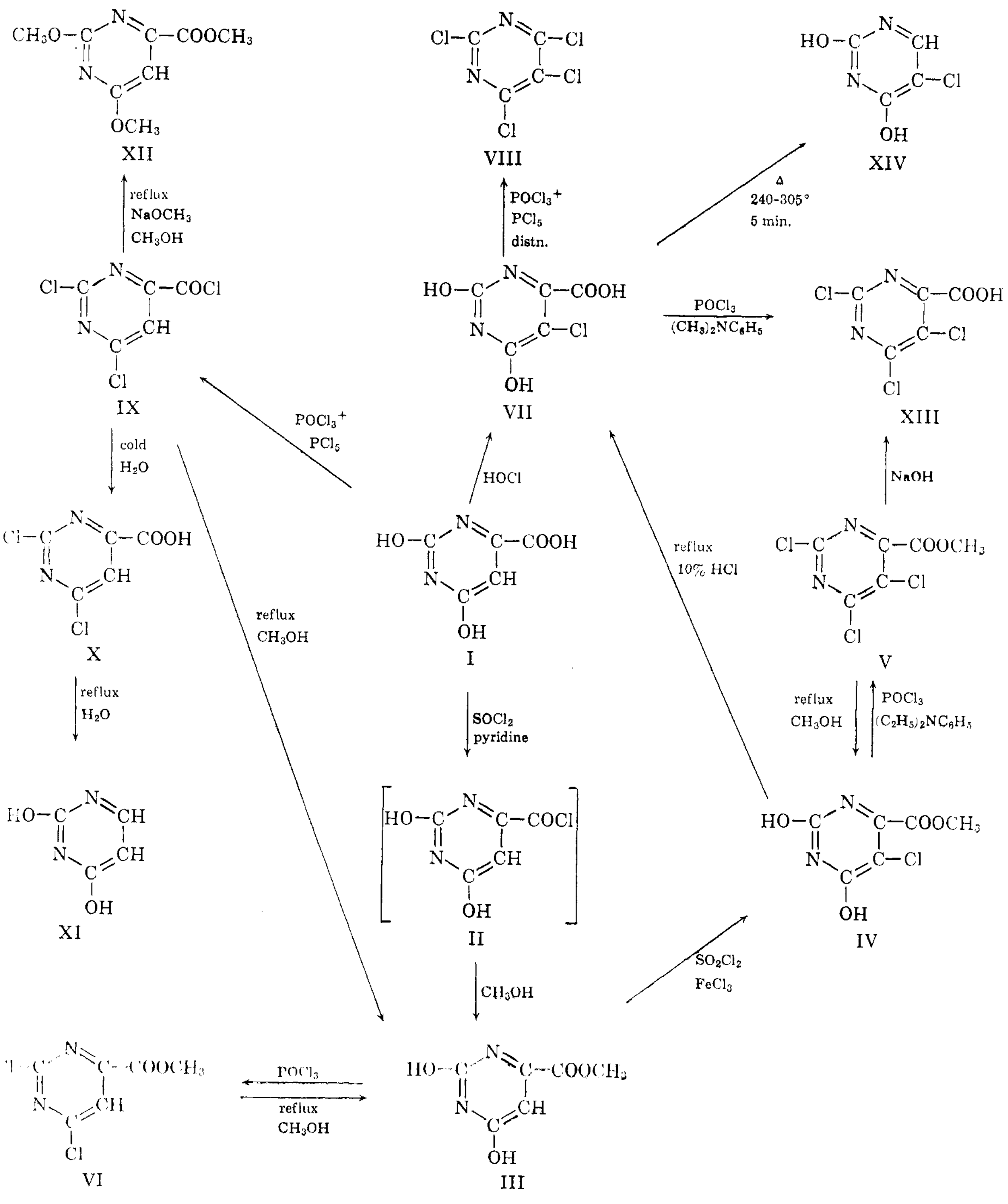
[1b] G. Biscaro and E. Belloni, *Ann. Soc. Chim. Milano*, **11**, 71 (1905).

[2] M. Bachstez, *Ber.*, **63A**, 1000 (1930).

[3] G. D. Daves, Jr., F. Baiocchi, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 2755 (1961).

[4] Orotic acid monohydrate was employed and offered no disadvantages over the anhydrous acid under the conditions of these reactions.

Scheme I



thionyl chloride present and to produce methyl orotate (III) in nearly quantitative yield. This synthesis compared favorably with the method[5,6] of direct esterification of I with methyl alcohol in the presence of hydrogen chloride or by the more recent method[3] of esterifying 4-hydroxy-2-methylthio-6-pyrimidinecarboxylic acid with methyl alcohol under a stream of hydrogen chloride followed by hydrolysis of the methylthio group by addition of aqueous hydrochloric acid. Methyl 2,6-dichloro-4-pyrimidinecarboxylate (VI) was prepared in 42% yield essentially as previously described[3] by treating III with phosphorus oxychloride.

Upon treating III with sulfuryl chloride in the presence of a catalytic quantity of ferric chloride,[7,8] methyl 5-chloroörotate (IV) was obtained in 89%

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[5] H. W. Wheeler, *Am. Chem. J.*, **38**, 358 (1907).

[6] H. Vanderhaeghe, *Bull. soc. chim. Belges*, **62**, 611 (1953).

[7] H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).

[8] H. Gershon, K. Dittmer, and R. Braun, *J. Org. Chem.*, **26**, 1874 (1961).

yield, m.p. 255–256°. IV was heated under reflux with a mixture of phosphorus oxychloride and diethylaniline, and yielded 47% of methyl 2,4,5-trichloro-6-pyrimidinecarboxylate (V), m.p. 56–58°. IV was hydrolyzed by means of 10% hydrochloric acid to yield 68% of 5-chloroörotic acid (VII) which decomposed at 286–288° with the evolution of carbon dioxide. On further heating of the solid in the capillary, a melting point of 316–318° dec. was observed. VII appeared to be identical with the 5-chloroörotic acid reported by Johnson.[9,10] A mixed melting point of VII, with a sample of 5-chloroörotic acid prepared by the hypochlorous acid method,[9] showed no depression in decomposition points. The identity of the material which decomposed at 316–318° was established by means of mixed melting points of VII with an authentic sample of 5-chlorouracil. No depression in the second decomposition point was observed. Also, XIV was obtained in 77% yield by heating VII at 290–305° for 5 min.

When VII was treated with phosphorus oxychloride and dimethylaniline followed by addition of phosphorus pentachloride, 3.7% of a product was obtained, after the usual work-up of the reaction mixture, whch boiled at 85–90° (1.8 mm.) and melted at 68–70°. The product was established as 2,4,5,6-tetrachloropyrimidine (VIII) by elemental analysis and by a mixed melting point with an authentic sample which was not depressed. The displacement of the carboxyl group by chlorine by means of the reaction with phosphorus oxychloride and phosphorus pentachloride seems to resemble the displacement of a sulfonic acid group by chlorine under similar conditions. Greenbaum[11] prepared 6-chloro-2,4-dimethoxypyrimidine by treating the corresponding sulfonic acid with phosphorus oxychloride and phosphorus pentachloride. It was assumed that the sulfonyl chloride was an intermediate step in the reaction. Another approach at preparing 2,5,6-trichloropyrimidine-4-carboxylic acid (XIII), was employed by treating VII with phosphorus oxychloride and diethylaniline. The yield of XIII was 15% and an analytical sample melted at 120°. Alkaline hydrolysis of V also gave XIII in low yield.

When orotic acid (I) was treated with phosphorus oxychloride and phosphorus pentachloride, with the intention of producing 2,6-dichloro-4-pyrimidinecarboxylic acid (X), a product was obtained by distilling the reaction mixture, which proved to be 2,4-dichloro-4-pyrimidinecarbonyl chloride (IX). The material was obtained in 64% yield, b.p. 109° (5 mm.). The structure was established by elemental analysis and by hydrolysis in cold water to yield 87% of X. Upon heating X under reflux in water it was decarboxylated and further hydrolyzed to uracil (XI). When I was treated similarly, no decarboxylation occurred, indicating that decarboxylation of X preceeded hydrolysis of the chlorine on the ring. The hydrolysis of 2,4-dichloropyrimidine to uracil is well known. Compound IX was heated under reflux with methyl alcohol and instead of producing VI as expected, III was obtained in 85% yield. Upon treating IX with three equivalents of sodium methoxide under reflux, methyl 2,6-dimethoxy-4-pyrimidinecarboxylate (XII) was obtained in 65% yield, m.p. 108–109°.

Since IX yielded III by refluxing with methyl alcohol, VI was treated in a similar manner and 78% of III was obtained. Similarly IV was obtained from V in 70% yield. It appears that these reactions involved a nucleophilic attack on the pyrimidine ring by the methyl alcohol. The byproduct of this reaction should be methyl chloride, but no attempt was made at isolation.

Experimental[12]

Orotyl Chloride (II).—A suspension was made of 87.0 g. (0.5 mole) of orotic acid monohydrate, 500 ml. of thionyl chloride, and 2.5 ml. of pyridine. It was agitated at room temperature for 7 hr. and heated under reflux for an additional 14 hr. The solid material was allowed to sediment on standing and a large portion of the unchanged thionyl chloride was removed by decantation. The product was satisfactory for esterification without purification.

Methyl Orotate (III).—To the orotyl chloride, as prepared above, was added 700 ml. of methyl alcohol dropwise with agitation. During the addition of the alcohol, the temperature of the reaction mixture fell due to the evolution of byproduct gases (methyl chloride, sulfur dioxide, and hydrogen chloride). Upon diminution of the rate of gas formation, the mixture was kept under reflux overnight and then cooled to 4–5°. The solid product was removed by filtration and washed with methyl alcohol and ether. The yield of ester was 80 g., m.p. 238°, lit.,[6] m.p. 240–242°. Upon evaporation of the mother liquors, an additional yield of 2.5 g., m.p. 230°, was obtained. The combined yield of product was 97%, based on orotic acid.

Methyl 5-Chloroörotate (IV).—To a solution of 34.0 g. (0.2 mole) of methyl orotate in 500 ml. of 5% acetic anhydride in glacial acetic acid was added a catalytic quantity of ferric chloride. The temperature was brought to 90–95° and 54.0 g. (0.4 mole) of sulfuryl chloride was added dropwise. Upon completion of addition of the sulfuryl chloride, the solution was slowly brought to reflux with agitation and heating was continued overnight until very little hydrogen chloride evolved. The solution was cooled to 18° and the product was removed by filtration, washed with acetic acid and then with water. The yield of product was 36.0 g. (89%), m.p. 250–255°. An analytical sample was obtained by recrystallization from methyl alcohol, m.p. 255–256°.

Anal. Calcd. for $C_6H_5N_2O_4Cl$: N, 13.70; Cl, 17.33. Found: N, 13.86; Cl, 17.15.

Methyl 2,5,6-Trichloro-4-pyrimidinecarboxylate (V).—A mixture of 20.5 g. (0.1 mole) of methyl 5-chloroörotate in 205 ml. of phosphorus oxychloride was prepared and kept at 15–20° while 77.5 g. (0.52 mole) of diethylaniline was added dropwise with agitation. The mixture was heated to boiling slowly and kept under reflux for 2.5 hr. Most of the phos-

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[9] T. B. Johnson, *J. Am. Chem. Soc.*, **65**, 1218 (1943).

[10] T. B. Johnson, *ibid.*, **66**, 146 (1944).

[11] S. B. Greenbaum, *ibid.*, **76**, 6052 (1954).

(12) All melting points are uncorrected and were taken in a Hershberg melting point apparatus. The ultraviolet spectra were taken with a Beckman DU. Orotic acid was purchased from Sigma Chemical Co., St. Louis 18, Missouri.

phorus oxychloride was removed by vacuum distillation and the residue was decomposed by ice. The product was extracted with ethyl ether, and the ether solution was washed with water, sodium bicarbonate solution, and water, and dried over sodium sulfate. Upon evaporation of the ether, 11.3 g. (47%) of product was obtained, m.p. 36–39°. The product was purified by sublimation and an analytical sample was prepared by crystallization from petroleum ether (b.p. 30–60°), m.p. 56–58°; $\lambda_{\max}^{CH_3OH}$ 282 mμ (log ε 3.67).

Anal. Calcd. for $C_6H_3N_2O_2Cl_2$: N, 11.60; Cl, 44.05. Found: N, 11.85; Cl, 43.97.

5-Chloroörotic Acid (VII).—A suspension of 2.42 g. (0.12 mole) of methyl 5-chloroörotate in 25 ml. of 10% hydrochloric acid was heated under reflux overnight. The product was removed by filtration and washed with acetone. The yield of VII was 1.6 g. (68%), m.p. 286–288° dec., lit.,[10] m.p. 295–296° dec. A second decomposition point was observed at 316–318° upon further heating the material in the capillary tube.

5-Chlorouracil (XIV).—One gram (0.0052 mole) of 5-chloroörotic acid was heated in a test tube immersed in an oil bath at 290–305° for 5 min. The material was dissolved in 2 *N* sodium hydroxide and treated twice with decolorizing carbon. The solution was acidified with 10% hydrochloric acid and allowed to cool in the refrigerator overnight. The product was obtained by filtration followed by a methyl alcohol rinse. The yield of XIV was 0.6 g. (77%), m.p. 318–318.5° dec., lit.,[13] m.p. 314–318° dec. No depression in decomposition point was observed when admixed with an authentic sample of 5-chlorouracil.

2,4,5,6-Tetrachloropyrimidine (VIII).—A mixture of 47.6 g. (0.25 mole) of 5-chloroörotic acid, 520 ml. of phosphorus oxychloride, and 155 g. (1.28 moles) of dimethylaniline was heated at reflux for 3 hr. After cooling the reaction mixture to 50–60°, 132 g. (0.75 mole) of phosphorus pentachloride was added and heating was resumed for an additional 8 hr. Most of the phosphorus oxychloride was removed under vacuum, and the residue was extracted five times with 300-ml. portions of ethyl ether which was decolorized with charcoal and evaporated. Upon distillation of the residue from the ether extract, a fraction was collected at 85–90° (1.8 mm.). The yield of product which solidified at room temperature was 2.0 g. (3.7%), m.p. 61–63°. An analytical sample was obtained by sublimation followed by crystallization from petroleum ether (b.p. 30–60°), m.p. 68–70°, lit.,[14] m.p. 67–68, 70°. No depression in melting point was observed on admixture with an authentic sample.

Anal. Calcd. for $C_4N_2Cl_4$: C, 22.05; N, 12.86; Cl, 65.09. Found: C, 21.86; N, 12.20; Cl, 64.80.

2,5,6-Trichloro-4-pyrimidinecarboxylic Acid (XIII).—A mixture of 5.72 g. (0.03 mole) of 5-chloroörotic acid, 100 ml. of phosphorus oxychloride, and 10 ml. of diethylaniline was heated under reflux for 3 hr. The reaction mixture was worked up in the usual manner similar to V. The yield of product was 1.2 g. (15%), m.p. 101–102°. An analytical sample was obtained from hexane, m.p. 120°; $\lambda_{\max}^{CH_3OH}$ 278 (log ε 3.70).

Anal. Calcd. for $C_5HN_2O_2Cl_3$: N, 12.32; Cl, 46.77. Found: N, 12.16; Cl, 46.38.

2,6-Dichloro-4-pyrimidinecarbonyl Chloride (IX).—Orotic acid monohydrate (104 g., 0.6 mole) was heated under reflux with 1040 ml. of phosphorus oxychloride overnight. To the cooled mixture was added 473 g. (2.25 mole) of phosphorus pentachloride and heating was resumed again overnight. On distillation, a fraction was collected at 76–77° (0.54–0.65 mm.). The yield of product was 82 g. (64%). An analytical sample was prepared by redistilling the product, b.p. 109° (5.0 mm.); $\lambda_{\max}^{cyclohexane}$ 287 (log ε 3.62).

Anal. Calcd. for $C_5HN_2OCl_3$:N, 13.24; Cl, 50.43. Found: N, 13.04; Cl, 50.43.

2,6-Dichloro-4-pyrimidinecarboxylic Acid (X).—2,6-Dichloro-4-pyrimidinecarbonyl chloride (21.2 g., 0.1 mole) was agitated for 1 hr. with water at room temperature. The crystalline product that formed was extracted with ethyl ether, washed with water, and the ether was removed by evaporation under vacuum. The yield of product was 16.8 g., m.p. 85–95°. An analytical sample was prepared by crystallization from ether followed by drying under vacuum at 70°, m.p. 105–107°, lit.,[3] m.p. 115–117°.

Anal. Calcd. for $C_5H_2N_2O_2Cl_2$: N, 14.51; Cl, 36.73. Found: N, 14.31; Cl, 36.79.

Methyl 2,6-Dimethoxy-4-pyrimidinecarboxylate (XII).—To 100 ml. of methyl alcohol was added 1.38 g. (0.06g.-atom) of sodium. To the solution of sodium methoxide was added 4.23 g. (0.02 mole) of 2,4-dichloro-6-pyrimidinecarbonyl chloride and the mixture was kept under reflux with agitation for 4 hr. An equal volume of water was added, and the mixture was cooled to 5°. The solid product was removed by filtration and washed free of chloride with distilled water and dried under vacuum over sulfuric acid overnight. The yield of product was 2.6 g. (65%), m.p. 108–109°. An analytical sample was obtained from isopropyl alcohol, m.p. 108–109°; $\lambda_{\max}^{CH_3OH}$ 284 (log ε 3.74).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.74; H, 5.04; N, 13.97.

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(13) J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 3478 (1955).

(14) Beilstein XXIII, p. 90.