[Contribution from the Venable Chemical Laboratory of the University of North Carolina]

The von Richter Reaction. IV. Identification of A Product from the Action of Potassium Cyanide on *p*-Nitroanisole[1]

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A neutral compound obtained from the action of potassium cyanide on *p*-nitroanisole has been identified as 4,4′-dimethoxy-2,2′-dicarbamylazoxybenzene (I).

Potassium cyanide in aqueous ethanol acts on many aromatic nitro compounds to give nitrogen-free carboxylic acids in which the carboxyl group occupies a position *ortho* to the original site of the nitro group.[1] This is the von Richter reaction. An example is the conversion of β-nitronaphthalene to α-naphthoic acid.

Yields obtained in von Richter reactions have never exceeded 50%, and frequently are less than 20%. Commonly, the expected carboxylic acid is accompanied by a large amount of acidic tar, apparently polymeric in nature.[3] The structure of such tars is not known, although it has been established in the case of acidic tars derived from *p*-chloronitrobenzene that their acidity is due to the presence of carboxyl groups which undoubtedly come from the potassium cyanide reagent.[3] Sometimes acidic tars are formed when the expected carboxylic acids are not.

In some cases, neutral, usually high-melting products have also been obtained[1] and sometimes such neutral products are dominant. Since knowledge of the identities of these neutral products and acidic tars might aid understanding of the mechanism of the von Richter reaction, we undertook to determine the structure of a neutral product obtained from the action of potassium cyanide on *p*-nitroanisole.

Bunnett, Cormack, and McKay[4] found that potassium cyanide and *p*-nitroanisole, heated in ethanol for one hour at 170–180°, formed *m*-anisic acid in 3% yield; they were able to recover 8.5% of unreacted *p*-nitroanisole. We found[1] that under reflux conditions no isolable amount of *m*-anisic acid was produced, but a considerable amount of acidic tar and also a yellow-orange neutral material were formed. This neutral material is the object of our present interest. Optimum conditions for its production appeared, from a set of exploratory runs, to involve 72 hours refluxing of a mixture of 100 g. of *p*-nitroanisole, 400 g. of potassium cyanide, and 1000 cc. of 48% ethanol. Under these conditions 20 g. of the neutral material was produced.

The neutral material (I) could be recrystallized from 2-ethoxyethanol; after recrystallization its color was yellow and it melted reproducibly at 230–234° with decomposition. Its elemental analysis was in agreement with the formula $C_{16}H_{16}N_4O_5$. It was found that it could be reduced by iron powder and ammonium chloride in aqueous ethanol; the product was a colorless basic compound (II) of m.p. 103°. The reduction product (II) was shown to be an aromatic primary amine when treatment with nitrous acid and then with an alkaline solution of β-naphthol produced an azo dye.

Hydrolysis of the neutral compound (I) with Claisen's alkali liberated ammonia and furnished a yellow acid (III) which melted with decomposition at 222–229° and had a neutralization equivalent of 174. (The neutralization equivalent of a dimethoxyazoxybenzenedicarboxylic acid is 172.) Attempted reduction of III with iron powder and ammonium chloride produced only tars.

Attempted hydrolysis of the reduction product (II) under alkaline conditions also produced tars, but hydrolysis with 20% hydrochloric acid yielded a small amount of an amino acid melting at 149–150°. (The reported[5] melting point of 2-amino-5-methoxybenzoic acid is 151°.)

Diazotization of II followed by treatment with cuprous chloride furnished a chlorine-containing neutral compound (IV) which could be hydrolyzed to a chlorine-containing acid (V) of m.p. 169–171°. (The reported[5] melting point of 2-chloro-5-methoxybenzoic acid is 172.5–173°.) Similarly, the Sandmeyer reaction on II using cuprous bromide furnished a bromine-containing neutral compound (VI) which was hydrolyzed to a bromine-containing acid (VII) of m.p. 159–160°. (The melting point of 2-bromo-5-methoxybenzoic acid is reported[5] to be 160°.) Deamination of II by diazotization and then hypophosphorous acid treatment yielded a white compound (VIII) of m.p. 131–132°. (The melting point of *m*-methoxybenzamide is reported[6] to be 133–134°.)

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[1] Paper III: Bunnett and Rauhut, *J. Org. Chem.*, **21**, 934 (1956).

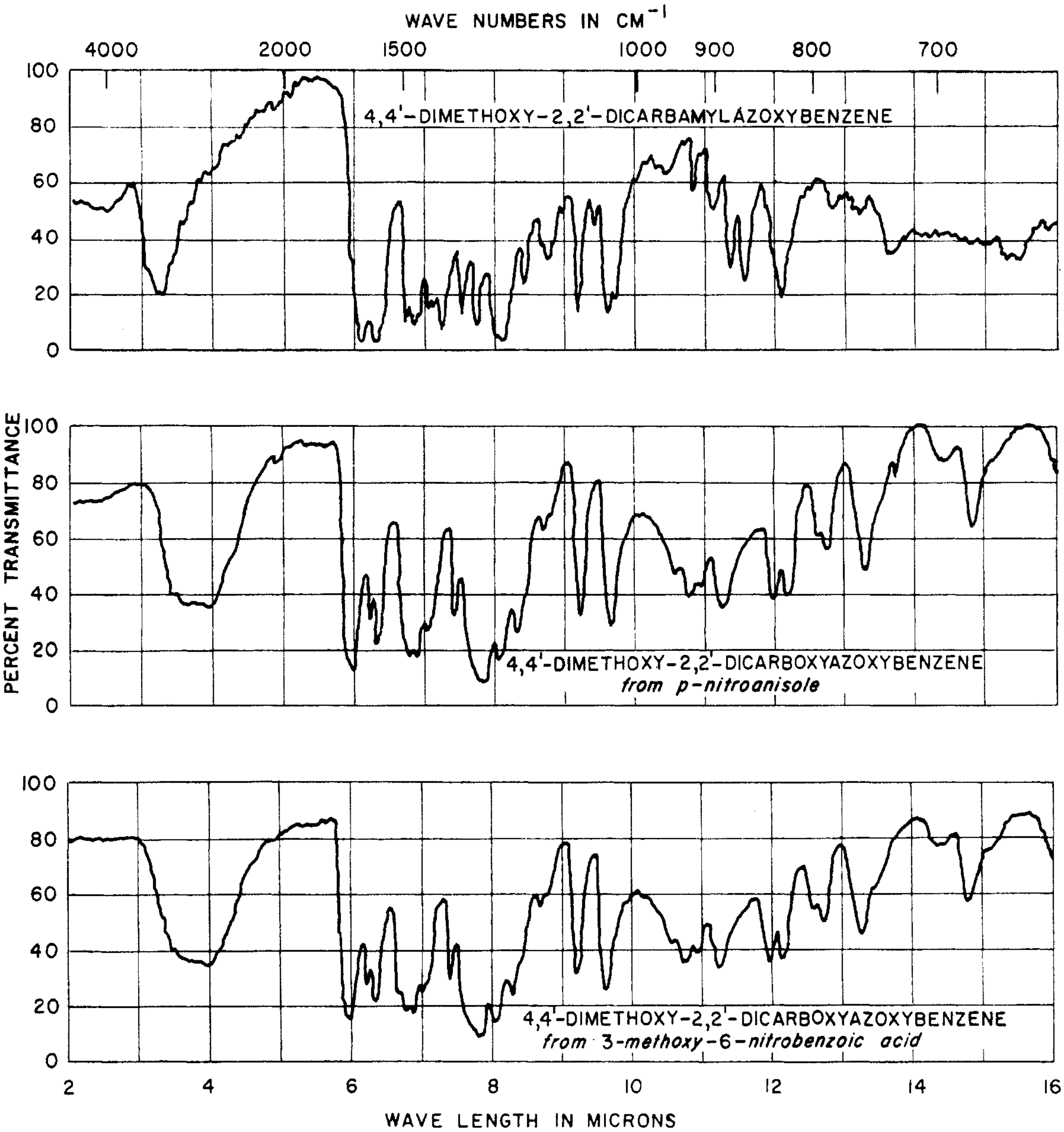
[2] American Viscose Fellow, 1954–1955. This paper is based on the Ph.D. Thesis of M. M. Rauhut, Oct. 1955.

[3] Bunnett, Rauhut, Knutson, and Bussell, *J. Am. Chem. Soc.*, **76**, 5755 (1954).

[4] Bunnett, Cormack and McKay, *J. Org. Chem.*, **15**, 481 (1950).

[5] Bachman and Picha, *J. Am. Chem. Soc.*, **68**, 1599 (1946).

[6] Brady and Dunn, *J. Chem. Soc.*, **123**, 1802 (1923); Shoppee, *J. Chem. Soc.*, 702 (1932).



These results coupled with analytical data for the compounds involved gave rise to the hypothesis that the yellow compound (I) obtained from *p*-nitroanisole is 4,4'-dimethoxy-2,2'-dicarbamylazoxybenzene, that its hydrolysis product (III) is 4,4'-dimethoxyazoxybenzene-2,2'-dicarboxylic acid, that its reduction product (II) is 2-amino-5-methoxybenzamide, and that the neutral compounds (IV and VI) obtained from II by the Sandmeyer reaction are 2-halo-5-methoxybenzamides. These structures appear in Chart I.

This hypothesis was supported by the infrared spectrum of I (Figure 1). Although we were unable to find the infrared absorption spectra of aromatic azoxy compounds in the literature, all the bands expected[7] of the other structural features of I appear in the expected places in the spectrum. Also, bands similar to those reported[8] for aliphatic azoxy compounds are present.

The structural assignment is also supported by the ultraviolet spectrum of I which shows an absorption maximum at 354 mμ. An analogous compound, 4,4'-dimethoxyazoxybenzene, has an absorption maximum at *ca.* 357 mμ.[9]

The correctness of this hypothesis was established by the unequivocal synthesis of II and III. Methyl *m*-chlorobenzoate was nitrated to yield methyl 2-nitro-5-chlorobenzoate which was converted, by treatment with methanolic potassium hydroxide, into the known 2-nitro-5-methoxybenzoic acid (IX). The amide (X) was prepared by

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(7) Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954.

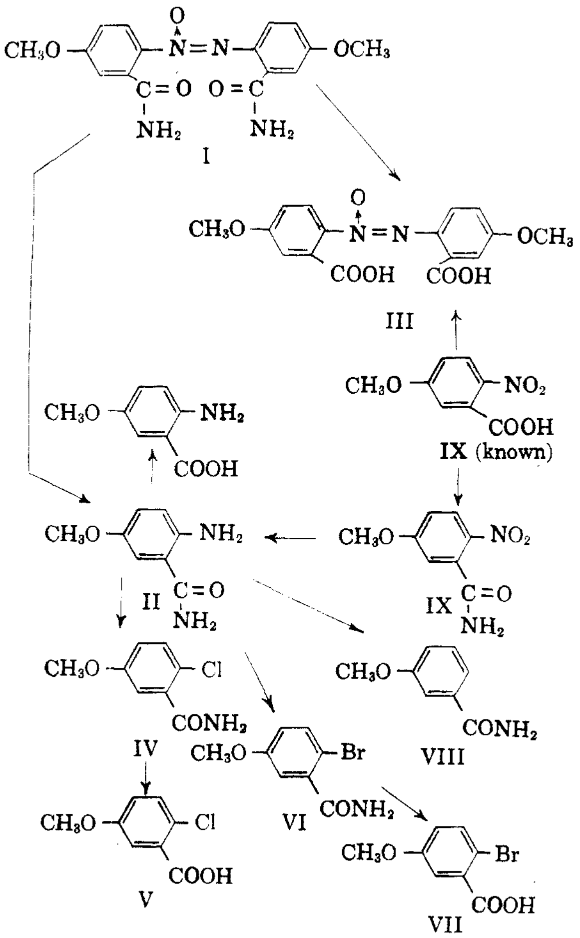
(8) Langley, Lythgoe, and Rayner, *J. Chem. Soc.*, 4191 (1952).

(9) Grammaticakis, *Bull. soc. chim.*, 951 (1951).

conventional means, and was reduced with iron and ammonium chloride to form 2-amino-5-methoxybenzamide (II) whose identity with II obtained by degradation of I was established by mixture melting point and by the identity of their infrared spectra.

Reduction of IX by glucose and potassium hydroxide in methanol furnished the corresponding azoxy compound, III, in small yield. The identity of this synthetic III with III from hydrolysis of I was established by the identity of their infrared spectra (Figs. 2 and 3) and their melting points.

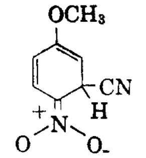
CHART I



Prior to the synthesis described above, 2-nitro-5-chlorobenzoic acid was synthesized by a more tedious route. Methyl *m*-nitrobenzoate was reduced and acetylated to form methyl 3-acetamidobenzoate, a new compound. Nitration of the latter followed by hydrolysis furnished 2-nitro-5-aminobenzoic acid from which 2-nitro-5-chlorobenzoic acid was obtained by the Sandmeyer reaction.

Discussion. The neutral product from the action of potassium cyanide on *p*-nitroanisole is identified as 4,4′-dimethoxy-2,2′-dicarbamylazoxybenzene (I). Plainly, the azoxy structure in this substance is derived from the nitro groups in two *p*-nitroanisole molecules and the carbamyl groups are derived from the cyanide reagent. Thus the production of I has involved these operations: attachment of the cyanide ion at a position *ortho* to the nitro group in *p*-nitroanisole, reduction to form an azoxy linkage (the adduct from cyanide ion and a nitro compound is in the state of oxidation of a nitrosobenzonitrile), and hydrolysis of the cyano group to an amide structure.

It is, however, difficult to say what the mechanism of the production of I is. There can be little question that the initial step is the attack of a cyanide ion on a position *ortho* to the nitro group to form adduct XI. Perhaps this then splits out the elements of hydroxide ion yielding 2-nitroso-5-methoxybenzonitrile which is then reduced to the corresponding azoxy compound which in turn is hydrolyzed to I. On the other hand, some more complicated mechanism may be involved, possibly involving rearrangement of XI to 2-nitroso-5-methoxybenzamide *via* intermediates similar in part to those proposed for the von Richter reaction in the following paper,[10] and finally reduction to I.



XI

EXPERIMENTAL[11]

Preparation of I *from p-nitroanisole. p*-Nitroanisole (100 g.), potassium cyanide (400 g.), 500 cc. of water, and 500 cc. of 95% ethanol were combined and refluxed for 72 hours. The dark red reaction mixture was cooled, diluted to 2500 cc., and filtered with suction. The dark filter cake was boiled with 200 cc. of acetone, the mixture was cooled, and the solid was collected on a suction filter. It was then recrystallized from 200 cc. of 2-ethoxyethanol, and the crystals were washed with 20 cc. of acetone and air-dried. Twenty grams (18%) of bright yellow plates, m.p. 230–234° with decomposition, were obtained.

Anal. Calc'd for $C_{16}H_{16}N_4O_5$: C, 55.80; H, 4.68; N, 16.27. Found: C, 56.12; H, 4.90; N, 16.36.

Hydrolysis of I. Compound I (2 g.) was refluxed on the steam-bath with 20 cc. of Claisen's alkali[12] for one hour. The reaction mixture was diluted with an equal volume of water, cooled to room temperature, and filtered. The filtrate was acidified and the precipitated acid was collected, washed with water, and recrystallized twice from dilute ethanol. One gram of III was obtained as yellow needles, m.p. 222–229° with decomposition.

Anal. Calc'd for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.07; N, 8.09. Found: C, 55.46; H, 4.35; N, 8.00.

Reduction of I. A mixture of 5.0 g. of I, 10 g. of iron powder, 40 cc. of 95% ethanol, 0.5 g. of ammonium chloride,

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(10) Bunnett and Rauhut, *J. Org. Chem.*, **21**, 944 (1956).

(11) Most analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Ill.

(12) Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 310.

and 10 cc. of water was heated under reflux on the steam-bath for 30 minutes. The condenser was removed and heating was continued until nearly all the solvent had evaporated. The residue was extracted with three 50-cc. portions of boiling benzene, and the combined extracts were evaporated to dryness. The resulting solid was recrystallized from a mixture of benzene and petroleum ether (b.p. 90–100°). Colorless crystals of II, m.p. 103°, were so obtained.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.06; N, 16.86. Found: C, 57.98; H, 5.98; N, 16.66.

The benzoyl derivative of II was prepared by a Schotten-Baumann procedure. After recrystallization from dilute ethanol, it melted at 198–200°.

Anal. Calc'd for $C_{15}H_{13}N_2O_3$: C, 66.90; H, 4.68; N, 10.40. Found: C, 66.91; H, 5.52; N, 10.37.

2-Amino-5-methoxybenzoic acid by hydrolysis of II. A portion of II (0.4 g.) was refluxed with 5 cc. of 20% hydrochloric acid for one hour. The resulting yellow reaction mixture was made slightly basic with ammonium hydroxide and then was neutralized with acetic acid. The solution was extracted with ether, the extracts were evaporated to dryness, and the residue was recrystallized twice from petroleum ether (b.p. 90–100°). A small amount of 2-amino-5-methoxybenzoic acid was obtained; m.p. 149–150° (lit.[5] m.p. 151°).

Products obtained from II *by Sandmeyer reactions.* A portion of II was diazotized and treated with a solution of cuprous chloride in hydrochloric acid according to the usual Sandmeyer procedure. The crude product was recrystallized twice from water; the resulting 2-chloro-5-methoxybenzamide (IV) melted at 134–135°.

Anal. Calc'd for $C_8H_8ClNO_2$: C, 51.75; H, 4.35; N, 7.54. Found: C, 52.24; H, 4.71; N, 7.44.

Two-tenths of a gram of the chloroamide (IV) was refluxed for 30 minutes with 2 cc. of Claisen's alkali.[12] The reaction mixture was diluted with an equal volume of water, acidified and filtered. The resulting 2-chloro-5-methoxybenzoic acid (V), after two recrystallizations from water, melted at 169–171° (lit.[5] m.p. 172.5–173°).

Another portion of the amino amide (II) was diazotized and treated with a solution of cuprous bromide in hydrobromic acid. The product (VI), after two recrystallizations from benzene, melted at 157° and was identified as 2-bromo-5-methoxybenzamide by hydrolysis to the acid as described below.

Anal. Calc'd for $C_8H_8BrNO_2$: C, 41.76; H, 3.50; N, 6.08. Found: C, 42.32; H, 3.52; N, 5.79.

Two-tenths of a gram of the bromo amide (VI) was refluxed for 30 minutes with 2 cc. of Claisen's alkali. The reaction mixture was diluted to 6 cc. and filtered. The filter cake was recrystallized twice from petroleum ether; the resulting 2-bromo-5-methoxybenzoic acid melted at 159–160° (lit.[5] m.p. 160°).

Deamination of II. One gram of II was diazotized and the diazonium salt was combined with 40 cc. of 50% hypophosphorous acid and kept 24 hours at 0°. The solution was extracted with ether, and the residue from evaporation of the extracts was recrystallized twice from petroleum ether. *m*-Methoxybenzamide (VIII) was obtained as white plates, m.p. 131–132° (lit.[6] m.p. 133–134°).

2-Nitro-5-methoxybenzoic acid (IX). Methyl *m*-chlorobenzoate (33 g.) was dissolved in 50 cc. of ice-cold concentrated sulfuric acid in a 200-cc. round-bottomed flask fitted with a dropping-funnel, a stirrer, and a thermometer. The solution was cooled to 5° by means of an ice-bath, and a mixture of 16 cc. of nitric acid (*sp. gr.* 1.42) and 16 cc. of concentrated sulfuric acid was added at such a rate that the temperature did not exceed 15°. After the addition, which required about an hour, the reaction mixture was allowed to stand at 15° for an additional 30 minutes. It was then poured onto ice; an oil separated and soon crystallized. The solid was collected, washed with two 20-cc. portions of ice-cold methanol, dried, distilled under reduced pressure, and recrystallized from methanol. Yield, 32 g. (77%) of methyl 2-nitro-5-chlorobenzoate, b.p. 135° (6 mm.), m.p. 45–47° (lit.[13] m.p. 48.5°).

A mixture of 30 g. of this ester, 45 g. of potassium hydroxide, 3 g. of manganese dioxide, and 300 cc. of absolute methanol was refluxed for 24 hours. The reaction mixture was filtered to remove manganese dioxide, neutralized with hydrochloric acid, filtered to remove potassium chloride, and evaporated nearly to dryness. Enough hot water was added to dissolve the oily residue, the solution was cooled and filtered, and the filter cake was dried and recrystallized from benzene. Yield, 6 g. (22%) of 2-nitro-5-methoxybenzoic acid, m.p. 133–135° (lit.[14] m.p. 132–133°).

2-Nitro-5-methoxybenzamide (X). A 0.5 g. portion of IX was intimately mixed with an equal weight of phosphorus pentachloride in a small test tube, and the resulting liquid was poured into 7 cc. of concentrated ammonium hydroxide. The resulting 2-nitro-5-methoxybenzamide (X) was recrystallized from water; purified, it melted at 154°.

Anal. Calc'd for $C_8H_8N_2O_4$: C, 49.00; H, 4.12; N, 14.29. Found: C, 48.90; H, 4.19; N, 14.33.

2-Amino-5-methoxybenzamide (II) *from* X. A mixture of X (0.25 g.), 0.5 g. of iron powder, 0.05 g. of ammonium chloride, 2 cc. of ethanol, and 0.5 cc. of water was heated on the steam-bath until nearly all the solvent had evaporated. The residue was extracted with three 3-cc. portions of hot benzene, and the combined extracts were cooled and filtered. The filter cake was recrystallized from a benzene–petroleum ether mixture. The II so obtained melted at 104–105°.

A mixture melting point with II obtained by reduction of I was not depressed, and there was excellent agreement between infrared spectra of the two samples of II.

III *from* IX. A mixture of 1.0 g. of 2-nitro-5-methoxybenzoic acid (IX), 0.5 g. of glucose, 2.0 g. of potassium hydroxide, and 10 cc. of methanol was refluxed for 15 hours. The reaction mixture was diluted to 20 cc. with water, cooled, and filtered. The collected solid was recrystallized from dilute ethanol; 0.1 g. of III was obtained as light yellow crystals, m.p. 222–229° with decomposition.

The identity of III thus obtained with III obtained by hydrolysis of I was established by comparison of their infrared spectra (Figures 2 and 3).

Methyl 3-acetamidobenzoate. Methyl 3-nitrobenzoate[15] (181 g.) was dissolved in 500 cc. of methanol, 170 g. of iron powder and 200 cc. of water containing 15 g. of ammonium chloride were added, and the mixture was refluxed with vigorous stirring for one hour. An additional 170 g. of iron powder was added, and heating was continued two hours longer. The hot mixture was filtered, and the filter cake was washed with several portions of hot methanol. The washings were combined with the main portion of the filtrate and most of the solvent was removed from the resulting solution by distillation. The oily residue was dissolved in a mixture of 2500 cc. of water and 83 cc. of concentrated hydrochloric acid, and the solution was heated to 50° and filtered to remove a trace of undissolved solid. Acetic anhydride (116 cc.) was stirred into the filtrate, and a solution of 150 g. of sodium acetate in 500 cc. of water was added at once in one portion with stirring. The resulting mixture was cooled to 5° with stirring and the precipitated solid was collected, washed with ice-water, and dried. The yield of white, methyl 3-acetamidobenzoate was 116 g. (60%); m.p. 133–135° (lit.[16] m.p. 136–137°).

Methyl 2-nitro-5-acetamidobenzoate. To an ice-cooled solution of 116 g. of methyl 3-acetamidobenzoate in 430 cc. of concentrated sulfuric acid, a solution of 58 cc. of nitric acid (*sp. gr.* 1.42) in 116 cc. of concentrated sulfuric acid was

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(13) Montagna, *Rec. trav. chim.*, **19**, 60 (1900).

(14) Rieche, *Ber.*, **22**, 2354 (1889).

(15) Kamm and Segur, *Org. Syntheses*, Coll. Vol. **1**, 2nd ed., 372 (1941).

(16) Ungnade and Henick, *J. Am. Chem. Soc.*, **64**, 1738 (1942).

added (with efficient stirring) at such a rate that the temperature did not rise above 5°. The addition took about an hour. The solution was allowed to stand at 0° for another hour, and then was poured over 1500 g. of ice. A viscous oil separated and soon crystallized. The resulting solid was recrystallized twice from benzene; 69 g. (46%) of methyl 2-nitro-5-acetamidobenzoate, m.p. 111–112° were so obtained.

Anal. Calc'd for $C_{10}H_{10}N_2O_5$: C, 50.40; H, 4.23; N, 11.82. Found: C, 50.53; H, 4.45; N, 11.82.

2-Nitro-5-chlorobenzoic acid. Methyl 2-nitro-5-acetamidobenzoate was hydrolyzed, by 15 minutes heating on the steam-bath with 20% sodium hydroxide solution, to 2-nitro-5-aminobenzoic acid, m.p. 232–234° (lit.[17] m.p. 235°), in 89% yield. This was diazotized, and the diazonium salt was treated with cuprous chloride in concentrated hydrochloric acid; there resulted 2-nitro-5-chlorobenzoic acid, m.p. 136–138° (lit.[18] m.p. 139°), in 28% yield.

Acknowledgments. We are grateful to the American Viscose Company and to the Office of Ordnance Research, U. S. Army, for financial assistance.

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(17) Mitchell and Hewitt, *J. Chem. Soc.*, 91, 1259 (1907).

(18) Holleman, *Rec. trav. chim.*, **24**, 194 (1905).