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

The von Richter Reaction. V. Evidence that Benzonitrile and Benzamide Derivatives are not Intermediates. The Mechanism of the Reaction[1,2]

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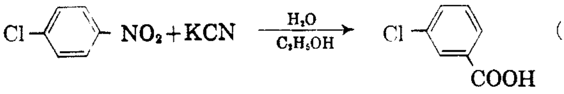
Neither α-naphthonitrile nor α-naphthamide is an intermediate in the production of α-naphthoic acid from β-nitronaphthalene by the von Richter reaction. Nor is *m*-chlorobenzonitrile or *m*-chlorobenzamide an intermediate in the production of *m*-chlorobenzoic acid from *p*-chloronitrobenzene. These results render unacceptable mechanisms previously proposed for the reaction. A mechanism in harmony with known facts is presented.

The von Richter reaction is a general reaction of aromatic nitro compounds with alkali metal cyanides; the product is a carboxylic acid in which the carboxyl group is situated *ortho* to the original position of the nitro group. An example is the reaction of *p*-chloronitrobenzene with potassium cyanide in 50% ethanol to form *m*-chlorobenzoic acid (equation 1).


(1)

von Richter[4] proposed a mechanism for the reaction as early as 1875, and Lobry de Bruyn and van Geuns[5] advanced another in 1904. A mechanism better in accord with modern theory was proposed by Bunnett, Cormack, and McKay[6] and later was modified[7] to accommodate new experimental results. Though these mechanisms varied considerably from one another, they had one feature in common: they all postulated that the carboxylic acid ultimately obtained was derived by hydrolysis from the corresponding nitrile. Thus, *m*-chlorobenzoic acid (equation 1) was believed to have been formed *via* *m*-chlorobenzonitrile as an intermediate.

It is true that substituted benzonitriles had never been isolated from von Richter reaction mixtures. But since the conditions of von Richter reactions were rather severe (temperature-wise or time-wise), it seemed not unreasonable that nitrile intermediates might be hydrolyzed in the reaction mixtures. This belief was strengthened by some experiments of Bunnett, Rauhut, Knutson, and Bussell[7] which indicated that *m*-chlorobenzonitrile was quantitatively hydrolyzed under the sealed tube conditions then commonly used for the reaction.

However, doubts that such nitriles could be intermediates were raised when it was discovered[8] that α-naphthoic acid in 13% yield is produced by the reaction of β-nitronaphthalene with potassium cyanide in only four hours in refluxing 48% ethanol. It seemed unlikely that α-naphthonitrile could be hydrolyzed under such mild conditions, especially considering that the medium was not strongly basic. These doubts were strengthened by discovery that α-naphthonitrile was not affected by four hours' refluxing with potassium cyanide in 48% ethanol; 90% of it was recovered unchanged.

A strenuous effort then was made to isolate α-naphthonitrile from an interrupted von Richter reaction of β-nitronaphthalene. The reaction was stopped after 1.5 hours refluxing, during which time only 6% of α-naphthoic acid had been formed. The neutral materials present were chromatographed on alumina. No α-naphthonitrile was found in the fractions of eluate in which it was expected, nor was any α-naphthamide found, but 15% of unreacted β-nitronaphthalene was recovered.

It was postulated that some component of the reaction mixture might be a catalyst *par excellence* for the hydrolysis of α-naphthonitrile to α-naphthoic acid. Nitrite ion, confirmed in this work to be a product of the von Richter reaction, was suspected but was found not to catalyze detectably the hydrolysis of α-naphthonitrile under the conditions used. It was then thought that some unknown intermediate in the von Richter reaction might be the postulated supercatalyst; however, from a von Richter reaction of β-nitronaphthalene to which α-naphthonitrile was added, only the normal yield (11%) of α-naphthoic acid from the nitro compound was obtained. Thus there was no evidence for hydrolysis of the nitrile to the acid under these conditions.

These experiments having shown that α-naphthonitrile is not an intermediate in the conversion of β-nitronaphthalene to α-naphthoic acid, we decided to reinvestigate the possibility that *m*-chlorobenzo-

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[2] Paper IV: Rauhut and Bunnett, *J. Org. Chem.*, **21**, 939 (1956).

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

[4] von Richter, *Ber.*, **8**, 1418 (1875).

[5] Lobry de Bruyn and van Geuns, *Rec. trav. chim.*, **23**, 26 (1904).

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

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

[8] Bunnett and Rauhut, *J. Org. Chem.*, **21**, 934 (1956).

nitrile might be an intermediate in equation 1. Bunnett, Rauhut, Knutson, and Bussell[7] had reported that *m*-chlorobenzonitrile was rapidly hydrolyzed to *m*-chlorobenzoic acid when present during a von Richter reaction of *p*-chloronitrobenzene (equation 1).

We first sought to isolate *m*-chlorobenzonitrile or *m*-chlorobenzamide from an interrupted sealed-tube von Richter reaction of *p*-chloronitrobenzene. Ten percent of *m*-chlorobenzoic acid was obtained in this reaction, and 73% unreacted nitro compound was recovered, but careful chromatographic examination of the neutral materials present in the reaction mixture did not reveal the presence of either the nitrile or the amide.

The action of potassium cyanide in 48% ethanol on *m*-chlorobenzonitrile was next investigated. After 40 minutes reaction at 150°, 33% of unreacted nitrile was recovered and 17% of *m*-chlorobenzoic acid was isolated. The fate of the other 50% of the starting nitrile was not determined, but the experiment establishes that the nitrile is not hydrolyzed with exceptional ease through the action of the alcoholic cyanide alone.

From a similar experiment but with sodium nitrite also present, *m*-chlorobenzamide was obtained in 69% yield, but neither the acid nor the nitrile was isolated. This suggests that nitrite ion accelerates the hydrolysis of the nitrile but retards hydrolysis of the amide.

The fate of *m*-chlorobenzonitrile when present during the sealed-tube von Richter reaction of *p*-chloronitrobenzene (equation 1) then was examined. Products were isolated by extraction, chromatography, and crystallization. From a normal von Richter reaction, without added nitrile, 31% of *m*-chlorobenzoic acid was obtained. From an identical reaction except that *m*-chlorobenzonitrile was added, an amount of acid was obtained equivalent to a 31% yield based on the nitro compound plus 9% based on the nitrile. In addition, *m*-chlorobenzamide was obtained in 47% yield, based on the nitrile. (In another nearly identical experiment, 60% of the amide was obtained.) Thus it is verified that *m*-chlorobenzonitrile *is* extensively hydrolyzed under sealed tube conditions at 150°, but to the *amide* for the most part. Since *m*-chlorobenzamide has not been isolated from von Richter reactions of *p*-chloronitrobenzene, even when assiduously sought, neither it nor *m*-chlorobenzonitrile can be an intermediate.

This pattern of hydrolysis principally to the amide is probably a consequence of nitrite ion liberated during the von Richter reaction. A similar pattern was observed (above) from the action of aqueous ethanolic cyanide-nitrite mixtures on *m*-chlorobenzonitrile.

The earlier report[7] that *m*-chlorobenzonitrile is hydrolyzed under sealed-tube von Richter reaction conditions is thus upheld, but the conclusion that the corresponding acid is produced is largely vitiated. How, we may ask, was the amide missed in the earlier work? The answer lies in the technique used: the reaction mixture was steam-distilled to remove unreacted nitrile and nitro compound, and then was acidified and further steam-distilled for a considerable time to sweep out the slightly volatile *m*-chlorobenzoic acid. The amide, having low volatility, was apparently hydrolyzed during the prolonged steam-distillations, and thus escaped detection. We repeated the experiment using steam-distillation to separate products, and duplicated in essence the results of the earlier paper.[7]

Other experiments. The possibility that formate ion, a product of hydrolysis of cyanide ion, might be the active reagent in the von Richter reaction had never been eliminated by experimental test. To test this possibility, we heated a mixture of *p*-chloronitrobenzene, formic acid, excess ammonium hydroxide, and ethanol in a sealed tube for one hour at 150°. No acidic products were discovered in the mixture after the period of heating, and 95% of the nitro compound was recovered.

The unlikely possibility that a cyano group might be introduced *ortho* to the nitro group to form an *o*-nitrobenzonitrile intermediate then was investigated. If such an intermediate was formed, 4-chloro-2-nitrobenzonitrile would be an intermediate in the production of *p*-chlorobenzoic acid from *m*-chloronitrobenzene.[9] However, we were unable to isolate *p*-chlorobenzoic acid from the reaction mixture obtained when this nitrile was heated with potassium cyanide in 48% ethanol for one hour at 150°. This unlikely mechanism can therefore be eliminated.

We found that addition of sodium hydroxide to von Richter reactions of *p*-chloronitrobenzene and *p*-nitrotoluene had no adverse affect on the yield. Similarly, potassium chlorate did not adversely affect the yield from *p*-chloronitrobenzene. Earlier,[7] cuprous oxide, manganese dioxide, and sodium nitrite were found not to interfere with the reaction, though potassium ferricyanide and sodium sulfite blocked the formation of *m*-chlorobenzoic acid.

Discussion. We have presented evidence that α-naphthonitrile and *m*-chlorobenzonitrile are not intermediates in the formation of, respectively, α-naphthoic acid and *m*-chlorobenzoic acid by the von Richter reaction. Nor are the corresponding amides intermediates. From this we surmise that in general the benzoic acid derivatives formed in the von Richter reaction are not formed *via* the corresponding nitriles or amides.

Since all previous mechanisms had assumed the opposite, none of them can be valid in its entirety.

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[9] Actually, *m*-chloronitrobenzene was reported by von Richter, *Ber.*, **4**, 459 (1871), to give *o*-chlorobenzoic acid, though it is quite possible that some *p*-chlorobenzoic acid was also formed.

We must bear in mind, in formulating an acceptable mechanism, that it must satisfactorily account for the following facts:

a. The carboxyl group appears without known exception *ortho* to the position vacated by the nitro group.[6,7,8]

b. Hydrogen from hydroxyl groups in the solvent is incorporated during the reaction.[7]

c. The benzoic acids obtained are not formed *via* hydrolysis of the corresponding nitriles or amides.

d. Nitrite ion is a by-product.

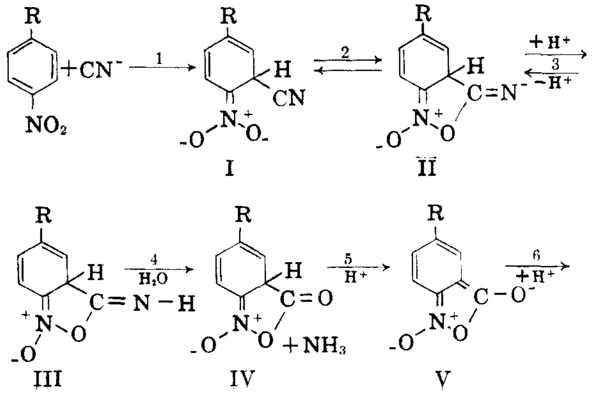
e. Substituents *ortho* to the nitro group retard but do not always prohibit the reaction.[6,7]

f. Substituents *meta* or *para* to the nitro group generally prohibit the reaction if their electronic effect on either position *ortho* to the nitro group can be expressed by a Hammett *sigma* constant of less than -0.2.[8]

g. Substituents *meta* or *para* to the nitro group whose electronic effect on either position *ortho* to the nitro group can be expressed by a Hammett *sigma* constant of greater than 0.6 generally favor reaction with cyanide ion but divert the reaction from the formation of benzoic acids.[8]

h. Tarry, acidic by-products whose carboxyl groups appear to be derived from the cyanide reagent usually are formed,[7] and sometimes there are also neutral by-products.[8] One of the latter has been identified.[2] The tarry acids are probably formed from some intermediate in the von Richter reaction, but the evidence for this proposition is not conclusive.

The mechanism shown in Chart I accounts for the above facts. Step 1 is the same initial step as proposed and discussed in an earlier paper in this series.[6] It is apparently a slow step, and its rate can be decreased by strongly electron-releasing substituents (fact *f*) or by substituents *ortho* to the nitro group (fact *e*). The latter interfere with the nitro group in I becoming coplanar with the benzene ring.



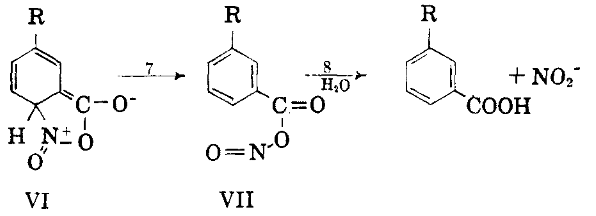
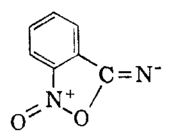


CHART I

Mechanism for the Formation of a *m*-Substituted Benzoic Acid from a *p*-Substituted Nitrobenzene *via* the von Richter Reaction.

The base-catalyzed addition of alcohols to nitriles to form imino-esters[10] is analogous to steps 2 and 3. That local interaction of a nitro group with an *ortho*-situated cyano group can occur in a manner similar to step 2 is indicated by the discovery of Rupe and Vogeler[11] that hydrogenation of *o*-nitrobenzonitrile in ethanol-ethyl acetate solution gave *o*-aminobenz*amide*, whereas hydrogenation of *m*- and *p*-nitrobenzonitriles under similar conditions gave products (aminobenzaldimines) representing hydrogenation but not hydrolysis. The production of a hydrolyzed product from the *o*-isomer under non-hydrolyzing conditions is best rationalized by assumption of a local interaction to form VIII which suffers hydrogenolysis of its nitrogen-oxygen but not its carbon-oxygen bonds.



VIII

Step 4 is the hydrolysis of the "imino-anhydride" III, and can be considered analogous to the hydrolysis of imino-esters. Imino-esters decompose in aqueous acid to form ammonia and an ester, and with basic catalysis to form an alcohol and a nitrile. In neutral solution, the latter mode of decomposition is dominant but the former mode occurs to a small extent.[12] Since decomposition of III to form "an alcohol and a nitrile" would merely reverse steps 3 and 2 to regenerate I from which III could quickly be formed again, the least tendency to decompose to form ammonia would be sufficient to account for the formation of IV.

Step 5 is self-evidently feasible, especially since the medium is somewhat basic. The return of the proton to the position occupied by the nitro group (step 6) is also reasonable. The proton, it should be noted, comes from the solvent and thus step 6 accounts for the exchange of hydrogen between the aromatic nucleus and the medium (fact *b*).

Step 7 is analogous to the final stage in the nu-

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(10) Marshall and Acree, *Am. Chem. J.*, **49**, 127 (1913).

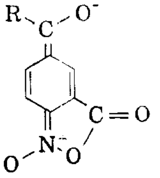
(11) Rupe and Vogeler, *Helv. Chim. Acta*, **8**, 832 (1925).

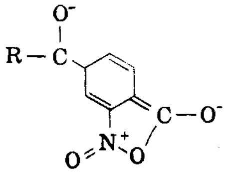
(12) Stieglitz, *Am. Chem. J.*, **39**, 29, 166 (1908).

cleophilic displacement of an aromatic nitro group.[13] The resulting carboxylic nitrous anhydride, VII, would be expected to hydrolyze rapidly to form nitrite ion (fact *d*) and the carboxylic acid which is isolated.

The mechanism clearly accounts for the fact (*a*) that the carboxyl group always appears specifically *ortho* to the position of the nitro group. It also avoids substituted benzonitriles or benzamides as intermediates, the two necessary stages of hydrolysis being accomplished in steps 4 and 8.

The unfavorable effect of strongly electron-attracting substituents (fact *g*) is perhaps due to overstabilization of intermediate V. Consideration of structures Va and Vb, which would be derived respectively from a *p*-nitrophenyl and a *m*-nitrophenyl ketone, shows that a group of strong −M effect either *meta* or *para* to the nitro group should stabilize intermediate V. If V reacts rapidly with a proton-donor (step 6) it gives the normal von Richter reaction, but if V is stabilized it may have time to react with some other substance present in the mixture to form one of the ubiquitous tars.


Va


Vb

This mechanism is similar in a few respects to the mechanism proposed by McEwen and Cobb[14] for the acid-catalyzed decomposition of Reissert compounds. Their publications were a stimulus to our thinking.

EXPERIMENTAL

Attempted isolation of α-naphthonitrile or α-naphthamide from a von Richter reaction. A mixture of 3.74 g. of β-nitronaphthalene,[15] m.p. 75–76.5°, 2.85 g. of potassium cyanide, 50 cc. of 95% ethanol, and 50 cc. of water was refluxed for 90 minutes. The dark mixture was poured onto about 100 g. of ice, 10 cc. of concentrated ammonium hydroxide was added, and the resulting suspension was extracted with 50-cc., 30-cc., and 30-cc. portions of chloroform. The dark brown chloroform layer separated cleanly from the orange-red water layer. The combined chloroform extracts were washed with 50 cc. of 2 *M* ammonium hydroxide and then boiled down nearly to dryness on the steam-bath. The aqueous layers were combined, acidified, boiled to expel hydrogen cyanide, and filtered while hot. A dark brown tar was collected on the filter paper, and an orange solid separated from the chilled filtrate. The orange solid was collected and additional orange-colored acid was recovered from the filtrate by a series of extractions. The combined orange acids were extracted with one 50-cc. and one 25-cc. portion of boiling carbon tetrachloride; much remained undissolved, but evaporation of the carbon tetrachloride extract furnished 0.28 g. (7.5%) of impure, orange α-naphthoic acid, m.p. 145–154°. After further purification, the product was white, had m.p. 159–160.5°, and weighed 0.21 g.

The neutral material from evaporation of the chloroform extracts (above) was chromatographed on alumina. Evaporation of the first fraction eluted by petroleum ether (b.p. 60–90°) yielded 0.26 g. of β-nitronaphthalene, m.p. 73.5–75.5°, not depressed on admixture with the starting material. This high melting point indicated the absence of α-naphthonitrile (see below). Subsequent fractions, eluted with various solvents, yielded other compounds including an unidentified white substance, m.p. 77.5–79.5° (depressed on admixture with β-nitronaphthalene), and an unidentified red-orange substance, m.p. 127.5–129°, but nothing melting at or near the melting point of α-naphthamide (202°).

In a blank experiment, a mixture of 0.24 g. of β-nitronaphthalene, 0.05 g. of α-naphthonitrile, and 0.04 g. of α-naphthamide was chromatographed similarly. The first fraction of petroleum ether-eluted material had m.p. 65.5–72°; this indicated that the nitrile and the nitro compound moved together through the column. A later fraction eluted with ethanol was pure α-naphthamide.

Behavior of α-naphthonitrile present during a von Richter reaction of β-nitronaphthalene. A mixture of 2.0 g. of β-nitronaphthalene, 1.0 g. of α-naphthonitrile, 1.7 g. of potassium cyanide, and 40 cc. of 48% ethanol was refluxed four hours. The reaction mixture was diluted to 200 cc. with water and extracted with ether. From the acidified water later, 1.16 g. of acidic material was obtained, and this was extracted with boiling carbon tetrachloride. From the carbon tetrachloride extract, 0.22 g. (11%) of α-naphthoic acid, m.p. 155–158°, was isolated. α-Naphthoic acid is soluble in hot carbon tetrachloride, and the insoluble acidic material is the familiar apparently polymeric by-product.

Attempts to hydrolyze α-naphthonitrile under von Richter reaction conditions. A mixture of 1.00 g. of α-naphthonitrile, 1.00 g. of potassium cyanide, and 20 cc. of 48% ethanol was refluxed four hours. By standard procedures, 0.90 g. (90%) of the nitrile, m.p. 34–36°, was recovered. No acidic product could be found.

In a second run, the above ingredients plus 0.50 g. of sodium nitrite were refluxed four hours. All of the nitrile (1.00 g.) was recovered from the mixture.

Attempted isolation of m-chlorobenzonitrile or m-chlorobenzamide from a von Richter reaction. p-Chloronitrobenzene (4.00 g.), 5.00 g. of potassium cyanide, and 60 cc. of 48% ethanol were heated in a sealed tube 38 minutes at 150°. The reaction mixture was diluted with water to 200 cc. and filtered; 2.75 g. (69%) of unreacted *p*-chloronitrobenzene, m.p. 82–83°, was collected on the filter. The filtrate was extracted with chloroform, and the extract was evaporated, furnishing 0.20 g. of solid residue which was chromatographed on alumina with benzene as eluent. The first fraction was evaporated to dryness, furnishing a solid of m.p. 78–81° which was thus more starting material. Nothing in the remaining fractions melted at or near the melting point of *m*-chlorobenzamide (134°). A blank experiment established that *m*-chlorobenzonitrile passed through an alumina column very quickly and appeared in the first fraction of eluate. That quite pure *p*-chloronitrobenzene was obtained in the first fraction shows, therefore, that at most a very tiny amount of *m*-chlorobenzonitrile could have been present. From the aqueous layer of the diluted reaction mixture, 0.40 g. (10%) of *m*-chlorobenzoic acid, m.p. 153–155°, was isolated.

Behavior of m-chlorobenzonitrile present during a von Richter reaction of p-chloronitrobenzene. p-Chloronitrobenzene (1.70 g.), *m*-chlorobenzonitrile (0.80 g.), potassium cyanide (5.00 g.), and 25 cc. of 48% ethanol were heated in a sealed tube at 147° for 40 minutes. Concurrently a second reaction, identical to the first except for the absence of the nitrile, was carried out as a control. At the end of the period of heating, both tubes were chilled in an ice-bath and the

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(13) Bunnett and Zahler, *Chem. Revs.*, **49**, 284 (1951).

(14) McEwen and Cobb, *Chem. Revs.*, **55**, 511 (1955); *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(15) Hodgson and Ward, *J. Chem. Soc.*, 127 (1947).

reaction mixtures were diluted with water to 150 cc. Ten cubic centimeters of 10% sodium hydroxide solution were added to each, and the solutions were filtered; from each was obtained 0.28 g. of neutral amorphous material. The filtrates then were extracted with three 30-cc. portions of chloroform, and the extracts were evaporated to dryness. Only in the nitrile experiment was there an appreciable residue; after crystallization from ethanol it melted at 129–133° (not depressed on admixture with authentic *m*-chlorobenzamide) and weighed 0.42 g. (47% based on the nitrile).

The aqueous solutions, after extraction with chloroform, were acidified and steam-distilled and acids were recovered from the steam-distillates as previously described.[6] From the control experiment, 0.53 g. (31%) of *m*-chlorobenzoic acid, m.p. 155–157°, was obtained. From the nitrile experiment, 0.62 g. of *m*-chlorobenzoic acid, m.p. 155–157°, was obtained.

A second nitrile experiment was carried out just like the above except that the neutral residue obtained by evaporation of the chloroform-extract was purified chromatographically. Results were much the same, but the yield of the amide, m.p. 134–136°, was 0.55 g. (60%).

A third nitrile experiment was performed like the first except that the products were separated by steam-distillation, as Bunnett, Rauhut, Knutson, and Bussell[17] had done. Steam-distillation of the reaction mixture furnished 0.23 g. (13%) of unreacted *p*-chloronitrobenzene, m.p. 82–83°. The residue was acidified and further steam-distilled, and from the distillate 1.25 g. of *m*-chlorobenzoic acid, m.p. 155–158°, was isolated; this is equivalent to quantitative hydrolysis of the nitrile plus a 20% yield from *p*-chloronitrobenzene. Comparison of this with the first and second nitrile experiments showed that the steam distillations brought about extensive hydrolysis of the *m*-chlorobenzamide actually present in the reaction mixture.

Attempts to hydrolyze m-chlorobenzonitrile under von Richter reaction conditions. *m*-Chlorobenzonitrile (1.5 g.), potassium cyanide (2.6 g.), and 75 cc. of 48% ethanol were heated in a sealed tube at 150° for 40 minutes. The reaction mixture was diluted to 200 cc., 10 cc. of 10% sodium hydroxide was added, and the solution was extracted with three 30-cc. portions of ether. The combined ether extracts were washed with a 5% sodium hydroxide solution and then with water, and were dried and evaporated; 0.50 g. (33%) of the nitrile, m.p. 39–41° was obtained. The aqueous layer from the original extractions was evaporated to 100 cc. and acidified; 0.30 g. (17%) of *m*-chlorobenzoic acid, m.p. 155–157°, was so obtained.

A second reaction was carried out just like the first except that 0.90 g. of sodium nitrite was also present in the reaction mixture. In this case neither *m*-chlorobenzonitrile nor *m*-chlorobenzoic acid could be isolated, but 1.18 g. (69%) of *m*-chlorobenzamide, m.p. 132–134° not depressed on admixture with an authentic sample, was obtained.

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