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

The von Richter Reaction. III. Substituent Effects[1,2]

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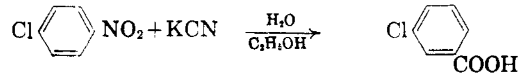
A general survey of the reactions of aqueous-alcoholic potassium cyanide with substituted nitrobenzenes has been made. In many cases the von Richter reaction occurs; in other cases it fails. In general, the von Richter reaction does not occur when the sum of the Hammett *sigma* values of substituents (excepting the nitro group which is lost) with respect to a position *ortho* to the nitro group is less than -0.2 or greater than 0.6. When the substituents are strongly electron-releasing (large negative σ values) the nitro compound is largely unattacked. When the substituents are strongly electron-attracting (large positive σ values) the nitro compound is wholly consumed but the reaction is diverted from the production of the expected acids.

The von Richter reaction is exemplified by the reaction (equation 1) of *p*-chloronitrobenzene with potassium cyanide in refluxing 50% ethanol to form *m*-chlorobenzoic acid. The reaction was discovered by von Richter[4] over 80 years ago, but it received little attention until the appearance of the earlier papers in the present series.[1,2] In these studies, we developed improved conditions for performing the reaction and demonstrated that it is general for aromatic nitro compounds, the general pattern being the elimination of a nitro group and the introduction of a carboxyl group *ortho* to the position formerly occupied by the nitro group. The reaction is thus a *cine*-substitution.[5] We also developed ideas regarding its mechanism and tested some of them experimentally.


(1)

Although the earlier work indicated that the von Richter reaction is general for aromatic nitro compounds, in the sense that it is not restricted to halonitrobenzenes, the question of substituent effects remained largely unexplored. We now report a general survey of substituent effects on the reaction.

We have examined the behavior, with potassium cyanide in refluxing 48% ethanol, of 21 additional nitro compounds, raising to 38 the number whose behavior with cyanide we have studied. We have also re-investigated a few compounds previously studied under other reaction conditions. The reactions which yielded identifiable acids are listed in Table I. Those which furnished no acids or unidentified acids, probably polymeric in nature, are listed in Table II.

TABLE I

Successful von Richter Reactions

Starting nitrobenzene deriv.	Product benzoic acid	Yield,[a] %	Starting material recovered, %	$\Sigma\sigma^b$
m-Methyl	*o*-Methyl	19	36	-0.17
p-Methyl	*m*-Methyl	3	61	$-.07$
p-Phenyl	*m*-Phenyl	0.5	94	[c]
p-Carboxylate	*m*-Carboxy	5	15	.10
p-Phenoxy	*m*-Phenoxy	6	52	.12[h]
p-Thiophenoxy[d]	*m*-Thiophenoxy	5	41	.14[h]
3-Bromo-4-methyl[e]	2-Bromo-3-methyl	13	0	.16
m-Trifluoromethyl[f]	*p*-Trifluoromethyl	8	0	.55
p-Benzoyl	*m*-Benzoyl	0.3	0	.31[h]
2,6-Dibromo	*m*-Bromo	1	90	
α-Nitronaphthalene	β-Naphthoic acid	0.7	0	
β-Nitronaphthalene[g]	α-Naphthoic acid	13	0	.17

[a] Conditions: 48 hrs. reflux in 48% ethanol unless otherwise indicated. [b] See text. [c] Yield probably limited by low solubility of starting material; not plotted in Fig. 1. [d] 82 hrs. refluxing. [e] 16 hrs. refluxing in 50% 2-ethoxyethanol. [f] 24 hrs. refluxing. [g] 4 hrs. refluxing. [h] σ values for *m*-OCH_3, *m*-SCH_3 and *m*-$COCH_3$ are given respectively, for *m*-OC_6H_5, *m*-SC_6H_5, and *m*-COC_6H_5, since σ values for the latter are not available.

A glance at Table I reveals that the von Richter reaction is indeed given by nitro derivatives of many classes of aromatic compounds. However, the yields are not very good and the reaction is not appealing as a synthetic method except perhaps in cases, such as the reactions of *p*-nitrodiphenyl sulfide and 2-bromo-4-nitrotoluene (Table I), in which it furnishes an otherwise difficultly accessible product in one step from a readily available starting material. The failure of the reaction to produce any isolable amount of the expected product in 14 cases (Table II) makes it still less attractive as a synthetic procedure.

A significant relation of yields to substituent effects is revealed in Figure 1, in which the log of the maximum yield of the normal von Richter product obtained from each substituted nitrobenzene stud-

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(1) Paper I: Bunnett, Cormack, and McKay, *J. Org. Chem.*, **15**, 481 (1950).

(2) Paper II: Bunnett, Rauhut, Knutson, and Bussell, *J. Am. Chem. Soc.*, **76**, 5755 (1954).

(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.*, **4**, 21, 459, 553 (1871); **7**, 1145 (1874); **8**, 1418 (1875).

(5) Bunnett and Zahler, *Chem. Revs.*, **49**, 382 (1951).

TABLE II

UNSUCCESSFUL VON RICHTER REACTIONS (reflux conditions[a])

Starting Compound	Procedure[a]	Starting material recovered, %	Acidic tar	Other neutral material	$\Sigma\sigma$[e]
m-Nitrodimethylaniline		75	Trace	None	−0.60
p-Nitrodimethylaniline		88	Trace	None	−.21
2-Nitrofluorene	B	75	Little	None	−.06
p-Fluoronitrobenzene		None	Much	[b]	.34
m-Nitroacetophenone	A and B	None	Much	None	.52
3-Bromo-4-fluoronitrobenzene	B	None	Much	None	.57
4-Nitropyridine	B	None	Little	None	.62
p-Nitrodiphenyl sulfone[c]	B	None	Little	Some	.65[f]
m-Nitrophenyl methyl sulfone	B	None	Much	None	.73
3,4,5-Triiodonitrobenzene	B	None	Little	Much	.91
4-Nitropyridine-1-oxide	B	None	Little	None	1.55
m-Nitroanisole		[d]	Trace	[d]	
p-Nitroanisole	A	None	Much	Much	
Nitrobenzene	A	75	Little	None	

[a] For detail on conditions, and for explanation of Procedures A and B, see the Experimental section. [b] *p*-Nitrophenetole (27%) was isolated. [c] 24 hrs. refluxing. [d] Not recorded. [e] See text. [f] σ for *m*-CH_3SO_2 is listed.

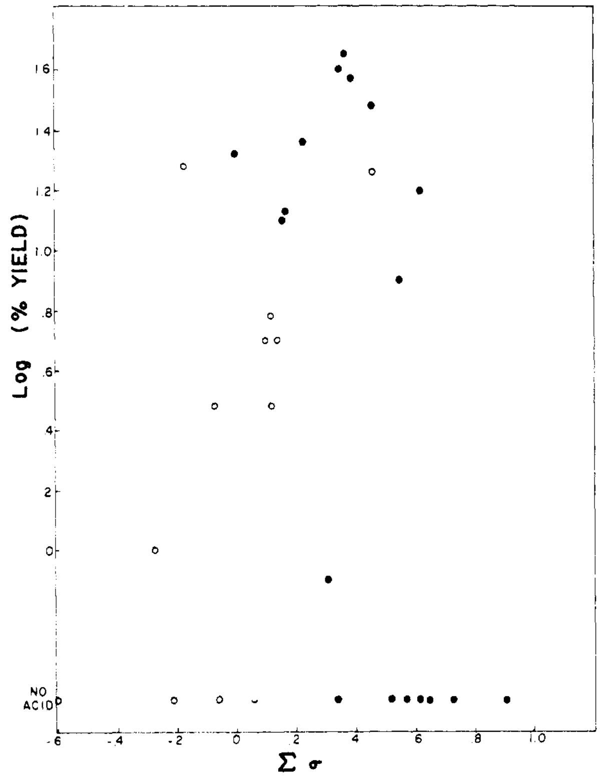

FIG. 1.—PLOT OF LOG (% YIELD) AGAINST $\Sigma\sigma$ FOR VON RICHTER REACTIONS OF *m*- AND *p*-SUBSTITUTED NITROBENZENES. ○ indicates that starting material was recovered; ● indicates that it was not. Data from Tables I and II are plotted only for those compounds for which σ values are listed. In addition, data from references 1 and 2 for the following nitrobenzene derivatives are plotted, with the σ values indicated being used: *m*-OCH_3, −0.27; H, 0.0; *m*-F, .06; *p*-OCH_3, .12; *m*-Br, .23; *p*-I, .35; *p*-Cl, .37; *p*-Br, .39; *3,5*-diCl, .46; *3,5*-diBr, .46; *3,4*-diBr, .62.

ied is plotted against the Hammett *sigma* constant[6] of the substituent with respect to the position taken by the carboxyl group. Compounds having substituents *ortho* to the nitro group are not included in Figure 1 because of the special inhibiting effect of such *ortho* substituents.[1] *Sigma* constants for substituents *ortho* to the position taken by the carboxyl group are assumed identical to *sigma* constants for the same substituents in the *para* position.[7] In the cases of compounds having more than one substituent in addition to the nitro group, the sum of the relevant *sigma* values is plotted. The σ-value of the nitro group which is replaced is not counted since it is a constant factor in all the reactions. For consistency, only data from this paper and the preceding two in this series[1,2] are considered.

The graphical plot indicates that yields are strongly dependent on substituent effects. The optimum substituent effect is realized when the *sigma* constant, or sum of *sigma* constants if several substituents are present, bearing on the position taken by the carboxyl group is about 0.37. Nitrobenzenes with substituents of less than the optimum *sigma* constant give lower yields, and from the reaction mixtures it is possible to recover some of the unreacted nitrobenzene derivatives. It thus appears that such substituents do not sufficiently activate the nucleophilic attack of cyanide ion on on the nitro compounds. Such behavior is not unexpected, since normal aromatic nucleophilic substitution reactions are known[8] to be favored strongly by substituents of high *sigma* constant.

Nitrobenzene derivatives bearing substituents of higher than the optimum *sigma* value also give lower yields. In these cases, however, unreacted nitrobenzene derivatives cannot be recovered from

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[6] Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, 1940, p. 186; Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[7] This assumption is not entirely correct, but is supported by work of Taft, *J. Am. Chem. Soc.*, **75**, 4231 (1953).

[8] Bunnett, Moe, and Knutson, *J. Am. Chem. Soc.*, **76**, 3936 (1954).

the reaction mixtures. Large amounts of apparently polymeric acidic by-products or unidentified neutral materials are formed, as noted in Table II. Thus the difficulty is not that attack of cyanide ion is opposed, but rather that the chemical species resulting from such attack undergo transformations which do not lead to the expected monomeric acids. It is possible that the proper von Richter reaction and the side-reactions leading to unidentified products involve one or more initial steps in common, and that some intermediate along the reaction path is diverted to by-products when strongly electron-attracting substituents are present.

The general rule that can be drawn from Figure 1 is that the von Richter reaction will probably not occur when the sum of the *sigma* values of substituents in respect to a position *ortho* to the nitro group is less than -0.2 or greater than 0.6, and that yields are likely to be very poor unless the sum of *sigma* values is between 0.2 and 0.5. There are a few exceptions to this rule, the most notable being the fluoro compounds, *m*- and *p*-fluoronitrobenzene and 3-bromo-4-fluoronitrobenzene, which did not give any of the expected acids although they all lie within the fruitful range of *sigma* values. The fluorine atom seems to exert some special unfavorable influence.

All the best yields in our experience have been obtained with mono- or di-halonitrobenzenes. This might lead one to suspect that the peak in Figure 1 is due to some unique influence of the halogens rather than to the magnitude of their electronic effects as represented by their *sigma* constants. That such is not the case is indicated by Holleman's[9] report that potassium *m*-nitrobenzenesulfonate and potassium cyanide react to form *o*- and *p*-sulfobenzoic acids in a total yield of 30%. Since σ for the *p*-sulfonate group is 0.38, the point for this compound would fall in the region of the peak in Figure 1 along with those for halonitrobenzenes.

Cadogan, Hey, and Williams[10] obtained a 5% yield of *m*-*tert*-butylbenzoic acid from *p*-*tert*-butylnitrobenzene. Were a point for this reaction plotted in Figure 1, it would also fall nicely in line with the general trend of the plot.

β-Nitronaphthalene is exceptionally reactive with potassium cyanide. The yield of α-naphthoic acid is only 13%, but this maximum yield is achieved in only four hours of refluxing in 48% ethanol and in the presence of much less cyanide than we have used with most nitro compounds. It is remarkable that an acid rather than a nitrile or an amide is produced under these mild conditions. A thorough examination of this reaction, reported in a following paper,[11] has been most instructive concerning the reaction mechanism.

A *m*-substituted nitrobenzene can suffer attack of cyanide at either of two positions *ortho* to the nitro group, forming an *o*-substituted benzoic acid if the cyanide attacks *ortho* to both substituents and a *p*-substituted benzoic acid if it attacks *ortho* to nitro but *para* to the other substituent. Products of attack *ortho* to the other substituent have been obtained from *m*-nitrotoluene, 2-bromo-4-nitrotoluene, 3,4-dibromonitrobenzene,[2] and β-nitronaphalene, while products of attack *para* to the other substituent have resulted from *m*-nitrobenzotrifluoride and *m*-nitroanisole.[1] A mixture of both types of products has been obtained from *m*-bromonitrobenzene[1] and potassium *m*-nitrobenzenesulfonate.[9] Except for the result from β-nitronaphthalene, it is difficult to see why these several reactions behave differently as they do.

Identification of products. Having gained confidence from previous work[1,2] that the carboxyl group always appears *ortho* to the position vacated by the nitro group, we frequently accepted agreement of melting points of found and expected products as satisfactory evidence of identity. In some cases we also prepared derivatives and compared their melting points with literature values. 2-Bromo-3-methylbenzoic acid is a new compound whose identity was deduced from two facts: (a) its melting point (135–137°) differs from that of the other probable product (4-bromo-3-methylbenzoic acid, m.p. 208–209°),[12] and (b) it can be oxidized to an acid having the same melting point as 2-bromoisophthalic acid.[13] *m*-Thiophenoxybenzoic acid, m.p. 107–109°, is also new; its structure is assigned by analogy with the products of other von Richter reactions, on the basis of analyses of itself and two derivatives, and with reference to the known[14] melting point (176–177°) of its *para* isomer.

Experimental conditions. All the reactions reported in Tables I and II were run in refluxing 48% ethanol, since these conditions were found[2] to be much more convenient and generally more effective than the sealed tube conditions used in earlier work. It is interesting to note, though, that nitrobenzene was not measurably converted to benzoic acid in refluxing 48% ethanol; in refluxing 90% ethylene glycol and in 48% ethanol at 160°, nitrobenzene was earlier[1,2] found to give benzoic acid in yields of 21% and 10%, respectively. This suggests that higher reaction temperatures might increase the yields in other cases in which unreacted starting materials can be recovered.

Refluxing 50% 2-ethoxyethanol (Cellosolve) was found to be a useful solvent for the reaction. The maximum yield obtained from *p*-chloronitrobenzene in this solvent was 35% which compares with yields

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[9] Holleman, *Rec. trav. chim.*, **24**, 194 (1905).

[10] Cadogan, Hey, and Williams, *J. Chem. Soc.*, 3352 (1954).

[11] Bunnett and Rauhut, *J. Org. Chem.*, **21**, 944 (1956).

[12] Remsen and Kuhara, *Am. Chem. J.*, **3**, 431 (1881).

[13] Coulson, *J. Chem. Soc.*, 1305 (1937).

[14] Szmant, Segedi, and Dudek, *J. Org. Chem.*, **18**, 745 (1953).

of about 45% in refluxing 48% ethanol. On the other hand, the reaction occurs faster in 50% Cellosolve apparently because of its higher boiling point. Thus, 31% of *m*-chlorobenzoic acid was obtained after only three hours refluxing in 50% Cellosolve whereas reflux periods of 24 to 48 hours are necessary to obtain the maximum yield in 48% ethanol. 2-Bromo-4-nitrotoluene gave 2-bromo-3-methylbenzoic acid in approximately equal yields in 48% ethanol and in 50% Cellosolve.

From *p*-chloronitrobenzene, a 9% yield of *m*-chlorobenzoic acid was obtained after 20 hours reaction in 50% acetpiperidide.

EXPERIMENTAL[15]

3-Bromo-4-fluoronitrobenzene, m.p. 58–59°, was prepared by brominating *p*-fluoronitrobenzene according to the general procedure of Derbyshire and Waters;[16] the reaction time was 20 hours. After recrystallization from ethanol, the yield of white crystals was 86%.

Anal. Calc'd for $C_6H_3BrFNO_2$: C, 32.77; H, 1.38; N, 6.36. Found: C, 32.91; H, 1.38; N, 6.19.

von Richter reactions. The nitro compound was combined with three to five times its weight of potassium cyanide in a weight of 48% ethanol on the order of five times the weight of the cyanide, and the mixture was refluxed for 48 hours unless otherwise noted. For example, 4.0 g. of *p*-nitrotoluene, 20.0 g. of potassium cyanide, and 100 cc. of 48% ethanol were refluxed 48 hours. After the period of refluxing, the reaction mixture was diluted to about three times its initial volume and neutral materials were removed usually by filtration and/or extraction with a solvent such as ether, or rarely by steam-distillation. In some cases the neutral material was starting material in a state of considerable purity. In all cases determined efforts were made to isolate starting nitro compound from the neutral material; often these efforts were successful but sometimes they were not. Some reactions gave considerable amounts of neutral products; with the exception of the neutral product from *p*-nitroanisole,[17] these were not identified, but none of them appeared to be the nitrile or amide corresponding to the acid expected to be formed in the reaction.

After the neutral materials had been removed, the diluted reaction mixture was acidified and the expected acid was sought by one of two general procedures: *Procedure A*, used to isolate acids expected to be steam-volatile, involved steam-distillation much as described previously.[1] *Procedure B:* the precipitated acidic material was collected by filtration, and the filtrate was extracted thrice with chloroform. The combined chloroform extracts were extracted with three 10-cc. portions of 5% sodium hydroxide, and any additional acidic material obtained by acidifying this basic extract was combined with the major portion collected by filtration. The acidic material thus obtained was dried and extracted in a Soxhlet extractor for eight hours with either petroleum ether (b.p. 90–100°) or carbon tetrachloride. The extract was evaporated to dryness and the residue (if any) was dissolved in 5% ammonium carbonate solution. The resulting solution was heated to boiling, treated with decolorizing charcoal, acidified, cooled, and filtered. When monomeric acids were formed, they were usually obtained in a condition of considerable purity by this procedure.

Below, we present information about the particular products obtained from the reactions listed in Table I: *m-Nitrotoluene*[18] (4.0 g.) furnished 0.74 g. (19%) of *o*-toluic acid, m.p. 105–106° (lit.[19] m.p. 104°), and 1.43 g. (36%) of *m*-nitrotoluene, m.p. 14–15°, was recovered. The acid was converted to *o*-toluamide, m.p. 138–139° (lit.[20] m.p. 140°).

p-Nitrotoluene (4.0 g.) furnished 0.13 g. (3%) of *m*-toluic acid, m.p. 110–113° (lit.[21] m.p. 110.5°) not depressed on admixture with an authentic sample, and 2.42 g. (60%) of unreacted *p*-nitrotoluene, m.p. 53–54°, was recovered.

p-Nitrobiphenyl (4.0 g.) was not wholly soluble in the 100 cc. of 48% ethanol used, even at reflux, and it is perhaps for this reason that 3.74 g. (94%) of *p*-nitrobiphenyl, m.p. 108–114°, could be recovered. Only 0.02 g. (0.5%) of *m*-phenylbenzoic acid, m.p. 158–160° (lit.[22] m.p. 161°) was isolated.

Sodium p-nitrobenzoate, from careful neutralization of 4.0 g. of *p*-nitrobenzoic acid,[18] gave a dark red reaction mixture which was acidified until a trace of precipitate appeared and then was treated repeatedly at the boiling point with decolorizing charcoal until the color was yellow. The solution then was acidified, and the precipitated material was collected, dried, and sublimed under a vacuum; the sublimate was 0.60 g. (15%) of unreacted *p*-nitrobenzoic acid, m.p. 235–238°. The residue from the sublimation was dissolved in dilute ammonium carbonate solution, the solution was decolorized with charcoal, and the acid was reprecipitated. Isophthalic acid (0.20 g.; 5%) of m.p. 347–348° (lit.[23] m.p. 348.5°) was so obtained.

p-Nitrodiphenyl ether (8.0 g.) furnished 0.40 g. of a yellow, methanol-insoluble material of m.p. 234–236° with decomposition, and 4.2 g. (52%) of *p*-nitrodiphenyl ether, m.p. 56–58°, were recovered. The yield of *m*-phenoxybenzoic acid, m.p. 138–143° (lit.[24] m.p. 145°), was 0.47 g. (6%); some of it was converted to *m*-phenoxybenzamide, m.p. 124–126° (lit.[25] m.p. 127°).

p-Nitrodiphenyl sulfide (20.0 g.) was recovered in the amount of 8.3 g. (41%), m.p. 53–55°, while 1.0 g (5%) of *m*-thiophenoxybenzoic acid, m.p. 104–107° was formed. After crystallization from water, the acid melted at 107–109°.

Anal. Calc'd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.37. Found: C, 67.96; H, 4.44.

m-Thiophenoxybenzamide, m.p. 132°, was prepared from the acid by conventional means.

Anal. Calc'd for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 67.93; H, 4.63; N, 6.11.

p-Phenylphenacyl *m*-thiophenoxybenzoate, m.p. 106°, was also prepared in a standard way.

Anal. Calc'd for $C_{27}H_{20}O_3S$: C, 76.39; H, 4.75. Found: C, 76.19; H, 4.82.

2-Bromo-4-nitrotoluene[26] (10.0 g.) furnished, after 17 hours refluxing in 48% ethanol, 1.2 g. (12%) of 2-bromo-3-methylbenzoic acid, m.p. 130–134° raised to 135–137° by recrystallization from petroleum ether.

Anal. Calc'd for $C_8H_7BrO_2$: C, 44.69; H, 3.28. Found: C, 44.65; H, 3.34.

2-Bromo-3-methylbenzamide, m.p. 186–187°, was prepared from the acid by conventional means.

Anal. Calc'd for C_8H_8BrNO: C, 44.88; H, 3.77; N, 6.54. Found: C, 44.81; H, 3.81; N, 6.51.

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[15] Analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Ill.

[16] Derbyshire and Waters, *J. Chem. Soc.*, 573 (1950).

[17] Rauhut and Bunnett, *J. Org. Chem.*, **21**, 939 (1956).

[18] Generously provided by E. I. du Pont de Nemours and Co.

[19] Jacobsen, *Ber.*, **10**, 1013 (1877).

[20] Hutchinson, *Ber.*, **24**, 174 (1891).

[21] Jacobsen, *Ber.*, **14**, 2349 (1881).

[22] Mayer, Ber., 46, 2587 (1913).

[23] Ullmann and Uzbachian, *Ber.*, **36**, 1798 (1903).

[24] Griess, *Ber.*, **21**, 980 (1888).

[25] Lock and Kempter, *Monatsh.*, **67**, 24 (1935).

[26] Prepared by a modification of the procedure of Cavill, *J. Soc. Chem. Ind. (London)*, **65**, 124 (1946).

p-Phenylphenacyl 2-bromo-3-methylbenzoate, m.p. 145–146°, was also prepared in a standard way.

Anal. Calc'd for $C_{22}H_{17}BrO_3$: C, 64.58; H, 4.18. Found: C, 64.36; H, 4.27.

The acid was oxidized by Coulson's[13] procedure to 2-bromoisophthalic acid, m.p. 215–217° (lit.[13] m.p. 218°).

m-Nitrobenzotrifluoride (4.0 g.) furnished 0.32 g. (8%) of *p*-trifluoromethylbenzoic acid, m.p. 218–220° (lit.[27] m.p. 219–220°).

p-Nitrobenzophenone (4.0 g.) furnished only 0.01 g. of m-benzoylbenzoic acid, m.p. 161–162° (lit.[28] m.p. 161°).

2,6-Dibromonitrobenzene (4.0 g.) furnished 0.03 g. (1%) of *m*-bromobenzoic acid, m.p. 143–147° (lit.[29] m.p. 154–155°); after admixture with authentic *m*-bromobenzoic acid, the m.p. was 147–150°. Unreacted 2,6-dibromonitrobenzene was recovered in the amount of 3.6 g. (90%).

α-Nitronaphthalene (4.0 g.) furnished 0.03 g. (1%) of *β*-naphthoic acid, m.p. 183–184° (lit.[30] m.p. 184°).

β-Nitronaphthalene (4.0 g.) furnished, after four hours refluxing with only 3.0 g. of potassium cyanide, 0.52 g. (13%) of *α*-naphthoic acid, m.p. 158–160° (lit.[31] m.p. 160°). A portion was converted to *α*-naphthamide, m.p. 201–202° (lit.[32] m.p. 202°).

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CHAPEL HILL, NORTH CAROLINA

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[27] Mooradian and Suter, *J. Am. Chem. Soc.*, **71**, 3508 (1949).

[28] Ador, *Ber.*, **13**, 320 (1880).

[29] Friedberg, *Ann.*, **158**, 19 (1871).

[30] Kailan, *Monatsh.*, **28**, 1080 (1907).

[31] Hofmann, *Ber.*, **1**, 39 (1868).

[32] Hofmann, *Compt. rend.*, **66**, 476 (1868).