A. Meijere, D. Kaufmann, and O. Schallner, *Tetrahedron Lett.,* 553 (1973); H. Prinzbach, S. Kagabu, and H. Fritz, *Angew. Chem.,* **86,** 522 (1974); *Angew. Chem., Int. Ed. Engl.,* **13,** 482 (1974); E. Vogel, E. Schmidbauer, and H.-J. Altenbach, *Angew. Chem.,* **86,** 818 (1974); *Angew. Chem., Int. Ed. Engl.,* **13,** 736 (1974); S. Kagabu and H. Prinzbach, *Tetrahedron Lett.,* 29 (1975).

(19) C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.,* **90,** 975 (1968).

(20) The other reported syntheses of 3[4] were from such a photooxygenation of 1 without isolation of 2 (11% yield) and from epoxidation of *cis*-benzene dioxide (10% yield).

(21) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.,* **91,** 5358 (1969).

(22) K. K. Maheshwari, P. de Mayo, and D. Wiegand, *Can. J. Chem.,* **48,** 3265 (1970).

(23) W. Adam, *Angew. Chem.,* **86,** 683 (1974); *Angew. Chem., Int. Ed. Engl.,* **13,** 619 (1974).

(24) K. Gollnick and G. O. Schenck in J. Hamer, "1,4-Cycloaddition Reactions", Academic Press, New York, N.Y., 1967, p 255.

(25) Presumably occurs through a diradical intermediate.[22]

(26) For an alternative synthesis of 5 see ref 14.

(27) *trans*-1,2,3,4-Diepoxycyclohexane has also been formed from catalytic reduction of 5 under similar conditions.[14]

(28) E. Vogel and H. Günther, *Angew. Chem.,* **79,** 429 (1967); *Angew. Chem., Int. Ed. Engl.,* **6,** 385 (1967).

(29) D. D. Traficante and J. A. Simms, *Rev. Sci. Instrum.,* **45,** 1063 (1974).

(30) The high-resolution mass spectra were provided by the Facility supported by National Institutes of Health Grant PR00317 (Principal Investigator Professor K. Biemann) from the Biotechnology Resources Branch Division of Research Resources.

(31) H_2O_2 was J. T. Baker reagent grade (30%). NaOCl was Clorox. Peroxide and hypochlorite solutions were standardized by reaction with KI solution and titration of I_2 formed with thiosulfate as described in I. M. Kolthoff and R. Belcher, "Volumetric Analysis", Vol. 3, Interscience, New York, N.Y., 1957, p 283.

(32) Model RPR 100 (Southern New England Ultraviolet Co., Middletown, Conn.): reactor barrel, 10 in. (diameter) by 15 in. (depth) with 16 lamps in a circular bank.

(33) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.,* **77,** 89 (1955).

The Nef-Type Transformation in Basic Solution

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The replacement of the nitro group of o-nitrobenzonitrile, which takes place when the substance is converted to 2-hydroxyisophthalonitrile by the action of sodium cyanide in Me_2SO, occurs via a Nef-type process of the cyanide ion adduct of the nitronitrile. The normal second product of the Nef reaction, nitrous oxide, is produced in yield comparable to that of the hydroxyisophthalonitrile. The similar conversions of p-nitrobenzonitrile and p-nitrobenzophenone to hydroxynitriles also produce nitrous oxide and hence proceed via the Nef route, although a part of the product from the nitro ketone may also form by the more complex path in which the cyanide ion adduct undergoes oxidation–reduction reactions via the ion radical with final displacement of the nitro group by hydroxide ion. The reactions constitute new examples of the rare occurrence of the Nef-type process in basic medium. For preparative use the nitrocyano compound may be produced in situ by reaction of sodium cyanide with a nitrohalo compound, e.g. o-nitrofluorobenzene, and converted on to the hydroxynitrile by reaction with excess sodium cyanide in the solution. Both the hydroxyisophthalonitriles prepared are rapidly converted to the high-melting, highly insoluble trimers, e.g., 2,4,6-tri-3-cyano-2-hydroxyphenyl-s-triazine from 2-hydroxyisophthalonitrile, by heating, conveniently, for preparative purposes, in dimethylaniline solution.

The direct conversion of an aromatic nitro compound to a cyanophenol in which the hydroxyl group is located on the carbon atom originally bearing the nitro group, occurring when the nitro compound is treated with sodium cyanide in an aprotic solvent, has been explained[1,2] as the result of displacement by hydroxide ion of the nitro group of an intermediate aromatic nitrocyano compound. Thus, 10-cyano-9-anthranol (4) was considered to form from 9-nitroanthracene (1) as the result of electron exchange of the Meisenheimer-type adduct (2), disproportionation of the


$$(1)$$
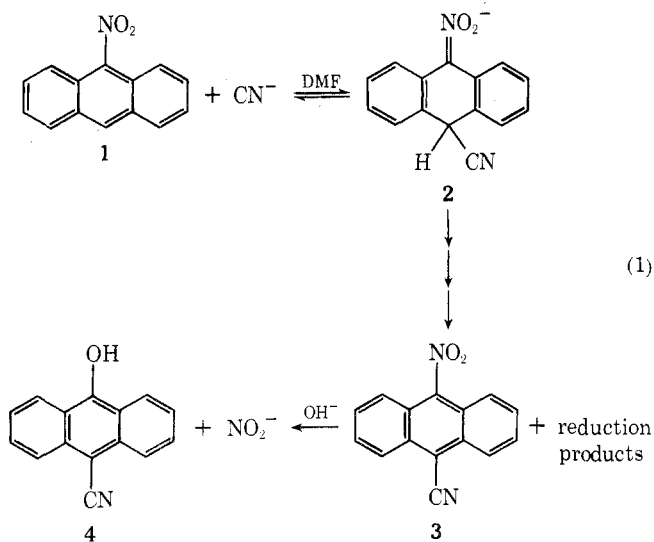
resulting radical with the formation of 10-cyano-9-nitroanthracene (3) and other products, and, finally, displacement of the nitro group of 3 by hydroxide ion. The hydroxide ion effecting the displacement was assumed to form from water adventitiously present in the solvent and/or reagent or produced in the oxidation–reduction reactions also occurring in the reaction solution.[1] A reduction product of 2, 10-cyano-9-aminoanthracene, could be isolated in yields up to 20%, and the proposed intermediate 3, an oxidation product of 2, could be isolated in trace amounts.

In a test of the substitution–displacement reaction on o-nitrobenzonitrile (5), carried out in Me_2SO with 2 equiv of sodium cyanide at 120° for 1 hr, the product mixture was much simpler than that from 9-nitroanthracene, and 2-hydroxyisophthalonitrile (8) could be isolated in 60% yield.[3] The absence of isolable amounts of reduction products suggested that the reaction occurred by a different course, perhaps one related to the Nef reaction. The Nef reaction itself has long been regarded as an exclusively acid-catalyzed transformation,[4,5] but recently the formation of levulinic acid from 4-nitrovalerate anion has been considered[6] an example of the Nef reaction occurring in basic medium; a gas presumed to be nitrous oxide, a normal product of the Nef reaction, was evolved.[6] The fact that the reaction also occurred with the anion of 4-nitro-3-methylvaleric acid but not with that of either 3-nitropropionic or of 6-nitrohexanoic acid led to the suggestion of a cyclic ester intermediate (carboxylate participation) in the formation of the levulinate anion.[6] No such intermediate could be involved in the transformation of the cyanide ad-

duct of a simple aromatic nitro compound, such as o-nitrobenzonitrile (5).

In a repetition of the o-nitrobenzonitrile reaction the gas evolved was swept by a stream of helium into a liquid nitrogen cooled trap, purified by vacuum distillation at $-80°$, and submitted to mass spectral examination. The gas proved to be nitrous oxide, the fragmentation patterns and the ratios of the peaks observed with the product and with an authentic sample being identical; it was isolated in 54% yield based on the nitronitrile employed (or approximately 90% based on the hydroxyisophthalonitrile isolated from the preparative test under the same conditions). A similar treatment of p-nitrobenzonitrile produced 4-hydroxyisophthalonitrile, along with a gas similarly shown to be nitrous oxide.

The key step in the reaction may be the ejection of hyponitrite ion from the Meisenheimer-type adduct (6) formed from o-nitrobenzonitrile (5) and cyanide ion, perhaps via the oxaziridine isomer (7), leading to the hydroxyisophthalonitrile (8) which can liberate nitrous oxide by protonating the hyponitrite anion. That nitrous oxide is formed as the reaction proceeds, rather than during the work-up, is shown by the experiment just cited, in which the gas formed during the heating period was collected. That the phenoxide anion 9 is present at the end of the reaction is indicated by the isolation of the methyl ether, in 30% yield, when a cooled reaction mixture was treated with methyl sulfate in the absence of any added base.


(2)
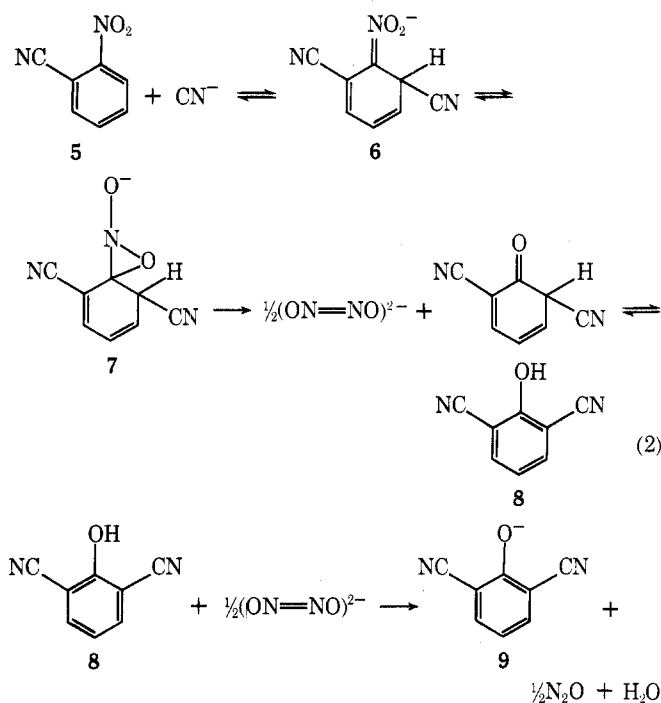
The identification of nitrous oxide as a principal product from the reaction of o- or p-nitrobenzonitrile makes it evident that the path differs from that of the reaction of 9-nitroanthracene. Further indication of different courses may be seen in the paramagnetic resonance spectra of the various reaction solutions. A solution of 9-nitroanthracene in DMF gave a strong EPR signal which diminished with time, interpreted as arising from radicals and ion radicals resulting from the participation of the adduct 2 in electron-transfer reactions.[1] Disproportionation of the radical corresponding to 2 leads to reduction products and to the intermediate 3, in a process similar to a number of reactions which have been studied.[7] However, a solution of o-nitrobenzonitrile (5) and sodium cyanide gave no detectable EPR signal, suggesting that the adduct (6) is rapidly re-

moved from the solution by another process (e.g., eq 2). Other simple benzene derivatives tested (m-nitrobenzonitrile, nitrobenzene, o- and p-nitrotoluenes, p-dinitrobenzene, and 1-nitronaphthalene) all gave strong signals, but they gave deeply colored reaction solutions from which no pure compounds could be isolated, probably because the radical process converted each of these substances into a large number of products. Nevertheless, the two reaction pathways are not necessarily mutually exclusive. Gorvin[2] found that p-nitrobenzophenone, which resembles the p-nitronitrile in having a stable electron-withdrawing group para to the nitro function, yields the expected cyanophenol along with colored by-products (considered to be azo and azoxy compounds, reduction products). He also found that when this reaction was conducted in Me_2SO containing methanol, some (10%) of the methyl ether, presumably formed by participation of methoxide ion in the displacement process (eq 1), could be isolated. In the present work the gas evolved in the p-nitrobenzophenone reaction was collected and found to be nitrous oxide. Thus, the cyanophenol from this nitro compound probably arises by both paths, with the Nef-type course predominating.

It should be possible to prepare the hydroxyisophthalonitriles from o- and p-nitrohalobenzenes in a single step by displacement of the halogen by cyanide ion and further reaction in situ of the nitrocyano compounds. When a reaction was run with equimolar amounts of o-nitrofluorobenzene and sodium cyanide the products isolated were 2-hydroxyisophthalonitrile (20%) and o-nitrobenzonitrile (14%), with 30% of the nitrofluoro compound being recovered. The figures indicate that the nitronitrile is consumed in the reactions of eq 2 at a rate somewhat faster than its rate of formation. The use of excess sodium cyanide resulted in the isolation of 2-hydroxyisophthalonitrile in 60% yield. p-Nitrofluorobenzene gave 4-hydroxyisophthalonitrile in somewhat lower yield (40%).

2-Hydroxyisophthalonitrile has been reported[8] to melt at a temperature above $350°$, far above the melting point ($98°$) of salicylonitrile.[9] In our observations, the hydroxyisophthalonitrile (8) appeared to undergo a change at temperatures near $250°$. Since salicylonitrile is known[9] to trimerize rapidly when heated to temperatures above $260°$, it appears that 2-hydroxyisophthalonitrile may trimerize so rapidly at temperatures near its melting point that no phase change is apparent and that the very high-melting substance is the triazine 10. Examination of the very stable, highly insoluble substance obtained confirmed the triazine structure (10). The triazine 10 was conveniently prepared in the analytically pure state by heating 8 in dimethylaniline. 4-Hydroxyisophthalonitrile also gave a trimer on heating, alone or in dimethylaniline. Although the monomer 8 is soluble in many common solvents and can be recrystallized from water, the trimer 10 proved to be completely insoluble in all the organic solvents tried except nitrobenzene and pyridine, and in these the solubility was slight. It did dissolve in cold concentrated sulfuric acid and in hot polyphosphoric acid, but not in dilute aqueous sodium hy-

(3)
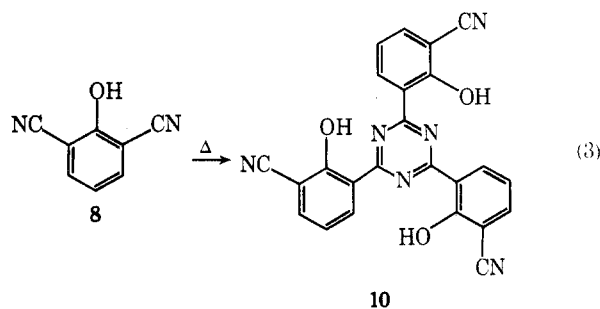
droxide. Probably because of the extremely low solubility, attempts to convert the triazine 10 to an acetyl derivative by heating with acetic anhydride and to a methyl ether by heating with methyl sulfate were unsuccessful.

Experimental Section

The high-resolution mass spectrometer and data processing equipment employed in the present study were provided by NIH Grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Sciences, respectively. Either a Perkin-Elmer 521 or a Beckman IR-12 spectrophotometer was used for ir spectra which were run as KBr disks. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH5 spectrometer at 70 eV. Microanalyses were performed by Mr. J. Nemeth and associates. Products were identified by comparison of ir and NMR spectra unless otherwise noted. All starting materials were either commercially available reagent grade and were used as received or were prepared in the laboratory by well-known synthetic routes. Me$_2$SO was stored over Linde Type 4A molecular sieves for 2 weeks before use.

1. 2-Hydroxyisophthalonitrile (8). A mixture of *o*-nitrobenzonitrile (1.48 g, 0.01 mol) and sodium cyanide (1.0 g, 0.02 mol) in 50 ml of Me$_2$SO was heated at 120° for 1 hr. The cooled solution was poured into 250 ml of dilute hydrochloric acid. The resulting red solution was filtered and extracted five times with 60-ml portions of methylene chloride. The combined extracts were decolorized and extracted four times with 20-ml portions of 5% sodium hydroxide solution. Acidification of the combined cooled extract to pH 3 gave a tan solid (0.80 g) which was recrystallized from water to give white crystals: mp >350°; ir 3200, 2242, 2238, 1600, 1570, 1460, 1320, 1255, 1215, 795 cm^{-1}.

Anal. Calcd for C$_8$H$_4$N$_2$O: C, 66.67; H, 2.80; N, 19.43. Found: C, 66.41; H, 2.86; N, 19.56.

2. Isolation of Nitrous Oxide from the Reaction of *o*-Nitrobenzonitrile and Sodium Cyanide. A solution of *o*-nitrobenzonitrile (1.48 g, 0.01 mol) in 50 ml of Me$_2$SO in a three-necked flask equipped with a gas inlet dipping into the liquid, a condenser, and a thermometer was thoroughly flushed with helium. The system was connected, via the condenser, to two liquid nitrogen cooled traps which in turn were connected to a high-vacuum line. After the system was thoroughly flushed with helium, sodium cyanide (1.0 g, 0.02 mol) was added and the mixture was heated to 120° for 1 hr with the helium flow continuing. At the end of this time the reaction flask was isolated from the high-vacuum line, which was then evacuated to 10^{-4} mm. The material which had collected in the liquid nitrogen traps was distilled through a trap cooled to −80°, recondensed in a liquid nitrogen trap, and then measured in the gaseous state. The amount of gas produced corresponded to 2.70 mmol. The mass spectrum of the gas was compared to the spectra of samples of carbon dioxide and nitrous oxide also purified in the same way. The experimental sample gave the following peaks: *m/e* 44, 30, 28, 27, 16, 14. The known nitrous oxide sample gave the same peaks with identical peak ratios and fragmentation patterns, and the carbon dioxide sample gave peaks at *m/e* 44, 28, and 16.

3. 2-Methoxyisophthalonitrile from *o*-Nitrobenzonitrile, Sodium Cyanide, and Methyl Sulfate. After a reaction mixture identical with that of 1 had been cooled to room temperature, dimethyl sulfate (2.37 ml, 0.025 mol) was added and the resulting solution was allowed to stand at room temperature for 3 hr. After acidification the mixture was extracted with methylene chloride, as in 1, and the methylene chloride solution was extracted with dilute sodium hydroxide. Acidification of the alkaline extract gave 0.22 g of 2-hydroxyisophthalonitrile. The remaining methylene chloride solution was washed well with water, concentrated, and placed on a silica gel column. Elution with benzene gave 0.47 g of 2-methoxyisophthalonitrile, mp 87–88°.

Anal. Calcd for C$_9$H$_6$N$_2$O: C, 68.34; H, 3.82; N, 17.71. Found: C, 68.31; H, 3.52; N, 17.50.

4. 4-Hydroxyisophthalonitrile and the Identification of Nitrous Oxide as Coproduct. A reaction of 1.48 g (0.01 mol) of *p*-nitrobenzonitrile and 1.0 g (0.02 mol) of sodium cyanide was carried out as described in 2. The gas evolved was collected, measured (3.6 mmol), and shown to be nitrous oxide by mass spectral examination (fragmentation patterns and ratios of peaks identical with those of authentic N$_2$O). The reaction mixture was worked up as described in 1 to give 0.9 g of tan solid which after two recrystallizations from water gave white crystals that did not melt below 350°: ir 3150, 2252, 2238, 1602, 1503, 1420, 910, 830, 413 cm^{-1}.

Anal. Calcd for C$_8$H$_4$N$_2$O: C, 66.67; H, 2.80; N, 19.43; mol wt, 144. Found: C, 66.36; H, 2.78; N, 19.47; mol wt, 144 (mass spectrum).

5. 5-Benzoylsalicylonitrile and Nitrous Oxide as a Coproduct. In apparatus similar to that used in 2 a mixture of 4-nitrobenzophenone (4.54 g, 20 mmol) and sodium cyanide (2.0 g, 40 mmol) was heated at 120° for 1 hr, cooled, and poured into 500 ml of ice water which had been acidified with 5 ml of concentrated hydrochloric acid. The aqueous mixture was extracted with ether and the ether solution was extracted with 5% sodium hydroxide. The dark oil which separated crystallized from benzene–toluene (1:2) to give 1.34 g (30%) of 5-benzoylsalicylonitrile which after recrystallization from benzene melted at 184–185° (lit.[10] 185–186°), and was of analytical purity; ir, 3270, 2235, 1610, 1310, 1285 and 705 cm^{-1}; mol wt by mass spectrum, 223 (calcd, 223). The gas evolved in this reaction was measured (2.29 mmol, 23%); it gave a mass spectrum identical with that of an authentic sample. The identification was confirmed by a high-resolution exact mass measurement (calcd for N$_2$O: *m/e* 44.0011; found, *m/e* 44.0011).

6. Hydroxyisophthalonitriles from Fluoronitrobenzenes and Sodium Cyanide in Me$_2$SO. A. A mixture of *o*-fluoronitrobenzene (1.0 ml, 0.01 mol) and sodium cyanide (1.0 g, 0.02 mol) in 50 ml of Me$_2$SO was heated at 120° for 2 hr under nitrogen. Workup similar to that described in 1 (addition to dilute acid, filtration, methylene chloride extraction, alkaline extraction of the methylene chloride solution, acidification, recrystallization from water) gave 0.87 g (60%) of 2-hydroxyisophthalonitrile identified by melting point, ir spectrum, and analysis.

B. A reaction mixture differing from the above only in containing 0.5 g (0.01 mol) of sodium cyanide was treated in the same way, yielding 0.28 g (20%) of 2-hydroxyisophthalonitrile, identified by melting point and ir. Concentration of the methylene chloride solution from this reaction, addition to a silica gel column, and elution with benzene gave 0.21 g (14%) of *o*-nitrobenzonitrile.

C. A reaction of *p*-fluoronitrobenzene under the conditions of 6A gave 4-hydroxyisophthalonitrile, identity confirmed by analysis, in 40% yield.

7. Trimerization of Hydroxyisophthalonitriles in Dimethylaniline. A. A solution of 0.5 g of 2-hydroxyisophthalonitrile in 2.5 ml of dimethylaniline was refluxed for 1 hr, at the end of which time an orange solid was present. After dilution with 100 ml of benzene, filtration, stirring with acetone, and filtration the yellow solid, **2,4,6-tri(3-cyano-2-hydroxyphenyl)-*s*-triazine,** was collected, dried, and analyzed: mp >350°; ir 2239, 1596, 1525, 1476, 1260, 791, 740 cm^{-1}.

Anal. Calcd for C$_{24}$H$_{12}$N$_6$O$_3$: C, 66.67; H, 2.80; N, 19.43; mol wt, 432. Found: C, 66.67; H, 2.81; N, 19.63; mol wt, 432 (mass spectrum).

B. The same procedure applied to 4-hydroxyisophthalonitrile produced **2,4,6-tri(5-cyano-2-hydroxyphenyl)-*s*-triazine:** mp >350°; ir 2232, 1580, 1440, 1300, 840 cm^{-1}.

Anal. Calcd for C$_{24}$H$_{12}$N$_6$O$_3$: C, 66.67; H, 2.80; N, 19.43. Found: C, 66.74; H, 2.79; N, 19.77.

References and Notes

(1) R. G. Landolt and H. R. Snyder, *J. Org. Chem.,* **33**, 403 (1968).
(2) J. H. Gorvin, *Chem. Commun.,* 1120 (1971).
(3) Most of our experiments with the nitrobenzonitriles were carried out before the publication of the same reaction by Gorvin (ref 2), who employed a slightly lower temperature (100°). A still lower temperature might be preferable, for the evolution of gas from the mixture containing the ortho isomer can be observed at about 80°.
(4) M. F. Hawthorne, *J. Am. Chem. Soc.,* **79**, 2510 (1957).
(5) N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.,* **87**, 1742 (1965).
(6) H. Wilson and E. S. Lewis, *J. Am. Chem. Soc.,* **94**, 2283 (1972).
(7) G. A. Russell and E. G. Janzen, *J. Am. Chem. Soc.,* **84**, 4153 (1962).
(8) D. B. Harper and R. L. Wain, *Ann. Appl. Biol.,* **64**, 395 (1969).
(9) M. M. Cousin and Volmar, *Bull. Soc. Chim. Fr.,* **15**, 416 (1914).
(10) A. Erndt, *Rocz. Chem.,* **36**, 921 (1962).