General Cleavage of N—N and N—O Bonds Using Nickel/Aluminum Alloy

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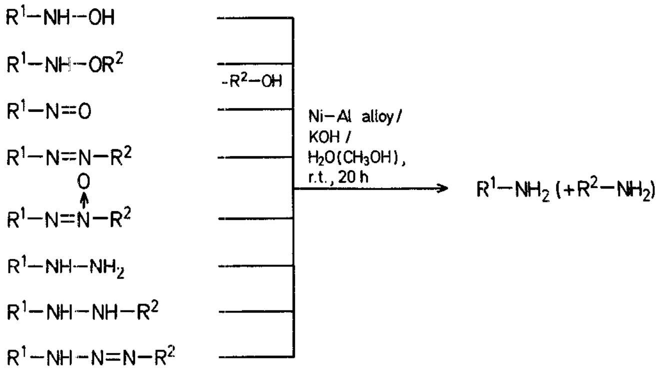
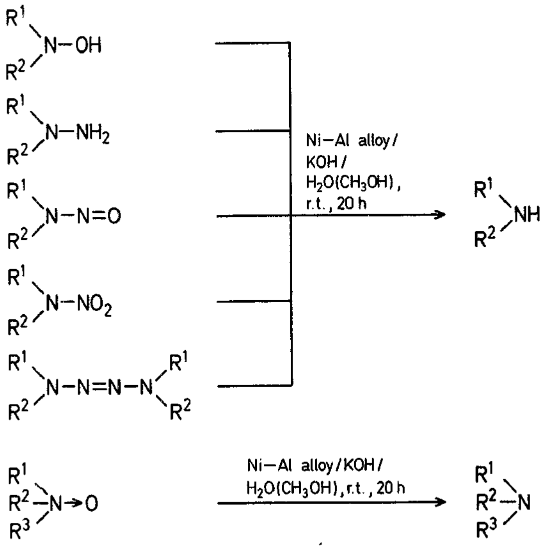
Addition of nickel/aluminum alloy to alkaline solutions of compounds containing N—N or N—O bonds appears to offer a general and convenient means for reducing such compounds to the corresponding amines. The method has been successfully applied to the reduction of nitrosamines, hydrazines, hydroxylamines, hydroxylamine ethers, triazenes, nitramines, *N*-oxides, tetrazenes, and nitroso, azo, and azoxy compounds.

We report here that nickel/aluminum alloy in base appears to be an excellent reagent for the convenient, quantitative, and general cleavage of N—N and N—O bonds. Using this technique we have successfully reduced nitrosamines, hydrazines, hydroxylamines, hydroxylamine ethers, triazenes, nitramines, *N*-oxides, tetrazenes, and nitroso, azo, and azoxy compounds in good yield, as summarized in the Scheme and the Table.

The cleavage of N—N and N—O bonds is frequently a key step in the manipulation of organic functionality; for example, important amine products can be prepared by the reductive cleavage of heterocycles formed in nitrone cycloaddition reactions[1]. As well as being generally useful for the interconversion of functional groups N—N and N—O cleavage can be used for the unmasking of amine synthons. Alkylation at the α-carbon of amines is a desirable reaction[2] and several methods have been suggested for accomplishing this. For example, it has been shown[3] that *N*-nitrosamines can be alkylated and the hydroxyalkylation of azo compounds has been demonstrated[4]. In addition, net alkylation of primary amines at the α-position via reaction of alkyllithium reagents with the corresponding azoxy derivatives has been effected[5]. The alkylated intermediates may then be cleaved to yield the alkylated amines. Since the nickel/aluminum technique can be used to reduce the functional groups found in all of these intermediates to their parent amines it should be a valuable addition to the chemistry of amine alkylation.

Besides providing a suitable technique for the cleavage of these intermediates, nickel/aluminum alloy in base should also prove valuable as a structure elucidation tool. Compounds such as cycasin, streptozocin, alanosine, and agaritine[6] have been isolated from biological sources, demonstrating that a variety of functional groups containing N—N





and/or N—O linkages may be found in nature. A simple and general means of converting unknown compounds similar to these into simpler or more easily characterizable fragments should be useful in their identification.

A third use of the method in the preparative chemistry laboratory is found in its utility for decontamination and disposal of certain hazardous compounds. Many nitrogen-nitrogen and nitrogen-oxygen compounds are powerful carcinogens[7,8] that may be converted to innocuous products using this technique. For example, we have shown that nitrosamines[9,10] and hydrazines[10,11] are completely degraded. Thus the technique is valuable not only because of its simplicity and versatility but also because of its applicability to problems in hazard control.

Nickel/aluminum alloy reduction[12] is simple to carry out and does not require forcing conditions or special apparatus. Compounds to be reduced are dissolved in water or methanol depending on solubility and mixed with an equal volume of 1 molar aqueous potassium hydroxide solution. Addition of nickel/aluminum alloy (in portions to avoid excessive frothing[12]) causes the reaction to proceed. After stirring overnight, it was found that the best procedure for isolation was to filter the reaction mixture through a pad of Celite, wash the spent nickel with water, and then distill the filtrate under a stream of nitrogen. The exhaust gases were passed through a hydrochloric acid trap and the distillation was continued almost to dryness. Then the distillate and the trap contents were combined, acidified with hydrochloric acid, and evaporated to give the crude amine hydrochloride that was purified by recrystallization from ethanol, ethanol/diethyl ether, or ethanol/water mixtures. In this way, nitrosamines, hydrazines, hydroxylamines, azo, azoxy, and nitro compounds were reduced to their parent amines in good overall yields as summarized in the Table. Problems were not normally encountered except when ammonia was also a reaction product. In these cases, several recrystallizations were generally required to separate the amine hydrochloride from ammonium chloride.

An alternative isolation procedure is to extract the filtrate with dichloromethane, and then recover the amine by distillation. This method worked best for amines that are not highly water-soluble and have moderately high boiling points. However, it should be recognized that some amines can react with dichloromethane[13].

When the starting material was only slightly soluble in water, it was initially taken up in methanol, and this solution was added to an equal volume of potassium hydroxide solution. The nickel/aluminum alloy was added in portions to this mixture, and the reduction was found to proceed smoothly. We have had success in reducing substrates which are poorly soluble in aqueous media. In the present work, we experienced no difficulty with preparative-scale reductions of such water-insoluble compounds as *N*-nitrosodiphenylamine and *N*-nitroso-di-*n*-butylamine when we added a methanolic solution of the substrate to an equal volume of 2 molar potassium hydroxide. In previous studies[9,10], we were able to effect facile, quantitative reduction in the presence of solvents such as dichloromethane and dimethyl sulfoxide which contain atoms (halide and sulfur) expected to compete strongly with the nitrosamine for reducing agent. The range of compounds reduced underlines the versatility of the method, and generally high yields were obtained. In some cases, the yield was probably lowered because of the volatility of the products, despite the fact that the exhaust gases from the distillation were passed through a hydrochloric acid trap with the aim of ensuring that none of the amine was lost.

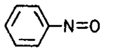
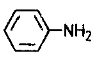
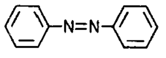
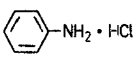
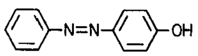
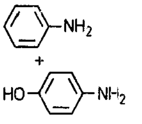
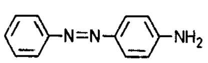
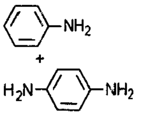
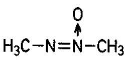
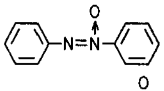
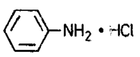
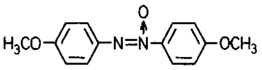
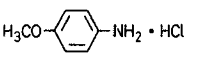
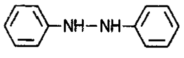
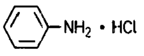
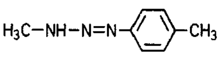
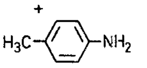
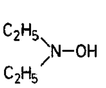
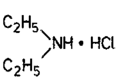
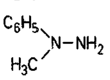
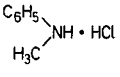
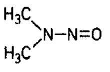
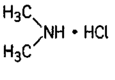
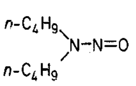
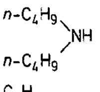
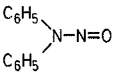
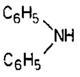
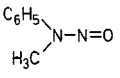
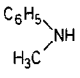
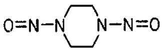
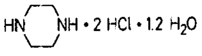
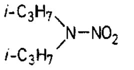
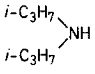
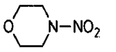
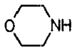
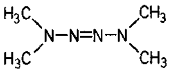
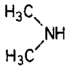
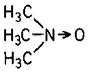
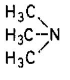
We believe that reduction with nickel/aluminum alloy in alkali has much to recommend it as a preparative method in organic chemistry. Resistance to rearrangements is one of the procedure's important advantages, for example. While lithium aluminum hydride and related reagents have been found to convert a benzoyl oxime to a mixture of isomeric amines, apparently resulting from a Beckman rearrangement, nickel/aluminum reduction produces only the unrearranged amine[14]. Nor does 1,2-diphenylhydrazine undergo the acid-catalyzed benzidine rearrangement[15] under these conditions. We carefully checked [11] the products of nickel/aluminum reduction of this hydrazine by gas chromatography but could find no trace of benzidine to the limit of detection (1 % of the theoretical yield), despite the fact that it is the major product when the hydrazine is reduced in acidic media[15]. Since benzidine is a powerful carcinogen[16], its absence from the hydrazine reduction mixture was most beneficial. Thus, the alkaline nature of the reducing system is found, in this case at least, to be advantageous.

Convenience and low cost are also among the method's great advantages. The alloy is readily available commercially and is, of course, inherently less expensive than the Raney catalysts made from it. The alloy does not appear to suffer any shelf-life limitations, unlike the Raney preparations[17].

When the reduction of nitrosamines was monitored by gas chromatography, we observed[9,18] that hydrazines were produced as transient intermediates although none remained in the final reaction mixture. We postulate that the initial reaction of the aluminum with the base reduces the nitrosamine to the hydrazine (which was the major product when only aluminum foil was used as the reductant[19]) and that the Raney nickel formed in the course of the reaction cleaves the hydrazine to the amine[20]. Interestingly, *N*-nitrosodiisopropylamine and *N*-aminodiisopropylamine were both detected as intermediates in the reduction of *N*-nitrodiisopropylamine while the only product in the final reaction mixture was diisopropylamine. Thus, the reduction of the *N*-nitro group, at least in this case, is also a stepwise process.

Together with reports in the literature that oximes[14,21], hydrazones[22], and nitro compounds[23] have been similarly con-

Table. Reduction of N—N and N—O Bonds Using Nickel/Aluminum Alloy in Base

Substrate	Product(s)	Yield [%]	m.p. [°C]	
			found	reported
$H_3C-NH-OH \cdot HCl$	$H_3C-NH_2 \cdot HCl$	77	234–235°	231–232°[31]
$H_3C-NH-OCH_3$	H_3C-NH_2 + H_3C-OH	88[a] + 100[a]	— —	— —
		104[a,b]	—	—
		79[b]	197–198°	199°[27]
		100[a,b] + 88[a,b]	— —	— —
		100[a,b] + 97[a,b]	— —	— —
 $H_3C-N=\overset{\overset{O}{\uparrow}}{N}-CH_3$	H_3C-NH_2	100[a]	—	—
		86[b]	197–198°	199°[27]
		58[b]	215–217°	215°[33]
		87[b]	198–199°	199°[27]
	H_3C-NH_2 + 	84[a,b] + 88[a,b]	— —	— —
 $(C_2H_5)_2N-OH$	 $(C_2H_5)_2NH \cdot HCl$	59	228–230°	226°[32]
 $(C_6H_5)(H_3C)N-NH_2$	 $(C_6H_5)(H_3C)NH \cdot HCl$	75[b]	125–126°	125–126°[30]
 $(H_3C)_2N-N=O$	 $(H_3C)_2NH \cdot HCl$	47	170–171°	171°[29]
 $(n\text{-}C_4H_9)_2N-N=O$	 $(n\text{-}C_4H_9)_2NH$	62[b,c]	—	—
 $(C_6H_5)_2N-N=O$	 $(C_6H_5)_2NH$	86[b]	51–52°	53°[28]
 $(C_6H_5)(H_3C)N-N=O$	 $(C_6H_5)(H_3C)NH$	60[c]	—	—
		78[d]	—	—
 $(i\text{-}C_3H_7)_2N-NO_2$	 $(i\text{-}C_3H_7)_2NH$	100[a,b]	—	—
		92[a]	—	—
 $(H_3C)_2N-N=N-N(CH_3)_2$	 $(H_3C)_2NH$	94[a]	—	—
 $(H_3C)_3N\rightarrow O$	 $(H_3C)_3N$	101[a]	—	—

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[a] Yields were determined by gas chromatography. Conditions are given in Experimental: analytical scale reactions.
[b] Methanol was used as a co-solvent.
[c] Isolated as free base; see experimental section for characterization data.
[d] Slowly decomposed on heating; see experimental section for characterization data.

verted to primary amines, it may be concluded from the above results that nickel/aluminum alloy in base is a versatile, convenient and general reagent for the cleavage of N—N and N—O bonds.

Warning. Many of the compounds mentioned in this paper, especially nitrosamines[7], hydrazines[8,24], azo[25], and azoxy compounds[26], are *carcinogenic*. They should be handled with due care using gloves in a properly functioning chemical fume hood. The nickel/aluminum alloy reductions *generate hydrogen* and should be done in an efficient hood. The nickel that is removed by filtration is potentially *pyrophoric*[12] and should not be sucked dry for extended periods. It should be allowed to dry on a metal tray in the absence of flammable solvents for 24 h before disposal.

The nitrosamines, 1,1,4,4-tetramethyltetrazene, and *N*-nitrodiisopropylamine were generously supplied by Dr. C.J. Michejda. We thank Pennwalt Corporation, Philadelphia, Pennsylvania, for a gift of *N*-hydroxydiethylamine. Nickel/aluminum alloy and all other reagents were obtained from Aldrich Chemical Company, Milwaukee, Wisconsin. Melting points were determined on an Electrothermal melting point apparatus. ^{1}H-N.M.R. spectra were obtained using a Varian XL100 operating at 100 MHz or a Perkin-Elmer R12B at 60 MHz. I.R. spectra were obtained on a Perkin-Elmer 467 spectrometer. Mass spectra were obtained on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The gas chromatograph was a Hewlett-Packard HP5830A fitted with a 1.8 m × 2 mm internal diameter silanized glass column using flame ionization detection. Peak areas were integrated by means of a built-in electronic integrator. The column packings were 10% Carbowax 20 M + 2% KOH on 80/100 Chromosorb W AW, 2% Carbowax 20 M + 1% KOH on 80/100 Supelcoport, 28% Pennwalt 223 + 4% KOH on 80/100 Gas Chrom R, and 3% SP2401-DB on 100/120 Supelcoport and column temperatures ranged from 60 to 150 °C. The carrier gas was nitrogen flowing at about 30 ml/min. The samples were injected directly onto a precolumn, which was changed periodically to protect the main column[9,11].

Cleavage of Azoxybenzene; Typical Preparative Scale Procedure with Product Isolated as the Hydrochloride:

Azoxybenzene (5.13 g, 25.9 mmol) in methanol (150 ml) is added to 1 molar aqueous potassium hydroxide solution (150 ml), and the mixture is stirred at room temperature in a 1 liter round-bottom flask fitted with a reflux condenser. Nickel/aluminum alloy (50 g) is added in portions over approximately 2 h, and the mixture is stirred for a further 18 h. At the end of this time, it is filtered through a pad of Celite 545 and washed through with water (500 ml). The spent nickel is placed on a metal tray and allowed to dry, in the absence of flammable solvents, for 24 h before being discarded with the solid waste. The filtrate is distilled under a stream of nitrogen. Nitrogen enters at the still head and exits at the receiver adapter. The exhaust gases are passed through a trap containing dilute hydrochloric acid. The flask contents are distilled almost to dryness (monitoring of the distillate by gas chromatography is helpful at this stage), then the distillate and the contents of the trap are combined, acidified with hydrochloric acid, and evaporated under reduced pressure to give a white solid. This is recrystallized from ethanol/diethyl ether to give *aniline hydrochloride* (5.10 g, m.p. 197–198 °C, lit.[27] m.p. 199 °C) as white crystals. A second crop (0.64 g, m.p. 197–198 °C) is obtained from the filtrate; total yield: 5.74 g (86%).

M.S.: *m/e* (relative intensity, %) = 93(100), 92(21), 66(26), 65(37), 63(12), 64(6), 54(7), 52(11), 51(9), 50(8).

Most procedures follow this pattern except that the compound to be reduced is frequently dissolved in water rather than methanol, depending on solubility. Those cases where methanol is used as a cosolvent are indicated in the Table.

Cleavage of *N*,*N*′-Dinitrosopiperazine:

Reduction of *N*,*N*′-dinitrosopiperazine (4.92 g, 34.2 mmol) as above with nickel/aluminum alloy (40 g) gives *piperazine dihydrochloride hydrate*; yield: 4.70 g (78%).

$C_4H_{10}N_2 \cdot 2HCl \cdot 1.2H_2O$	calc.	C 26.59	H 8.03	N 15.50
(180.7)	found	26.34	7.74	15.51

M.S.: *m/e* (relative intensity, %) = 86(53), 85(79), 83(18), 81(16), 71(12), 69(19), 67(12), 57(55), 56(57), 55(26), 44(100).

Cleavage of *N*-Nitrosodi-*n*-butylamine; Typical Procedure with Product Isolation by Extraction and Distillation:

N-Nitrosodi-*n*-butylamine (2.70 g, 17.1 mmol) is reduced as described above by nickel/aluminum alloy (30 g) in methanol (75 ml) and 2 molar aqueous potassium hydroxide solution (75 ml), and the filtrate is extracted three times with dichloromethane. Short-path distillation gives *di*-n-*butylamine* which is identified by spectroscopic techniques; yield: 1.37 g (62%).

M.S.: *m/e* (relative intensity, %) = 129(8), 88(5), 87(5), 86(100), 84(49), 73(5), 57(15), 56(8).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.0 (br. t, 6 H); 1.4 (br. m, 8 H); 2.6 ppm (br. t, 4 H).

I.R. (neat): ν = 3280 cm^{-1}.

Cleavage of *N*-Methyl-*N*-nitrosoaniline:

In an identical fashion, *N*-methyl-*N*-nitrosoaniline (3.37 g, 24.8 mmol) is reduced to N-*methylaniline*; yield: 1.58 g (60%).

M.S.: *m/e* (relative intensity, %) = 107(86), 106(100), 105(6), 104(7), 85(6), 84(19), 83(12), 79(21), 78(10), 77(29), 65(9), 57(7), 53(6), 52(6), 51(12), 50(5), 44(16).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 2.75 (s, 3 H); 3.6 (br. s, 1 H); 6.6 (m, 3 H); 7.2 ppm (m, 2 H).

I.R. (neat): ν = 3420, 1605, 1510 cm^{-1}.

N-Methylaniline (from 1-methyl-1-phenylhydrazine) was also isolated as the hydrochloride, as described above, and identified by its m.p.

Cleavage of *N*-Nitrosodiphenylamine; Typical Procedure with Product Isolation by Extraction and Recrystallization:

N-Nitrosodiphenylamine (9.93 g, 50.2 mmol) is reduced as described above by nickel/aluminum alloy (50 g) in methanol (200 ml) and 2 molar aqueous potassium hydroxide solution (200 ml). Extraction of the filtrate with dichloromethane gives, after evaporation of the solvent and recrystallization from aqueous ethanol, *diphenylamine*; yield: 7.30 g (86%); m.p. 51–52 °C (Ref.[28], m.p. 53 °C).

Analytical Scale Reactions; General Procedure:

The substrate (5 mg) and an equal amount of an inert internal standard (generally an alcohol) in methanol or water (0.5 ml) are added to 1 molar aqueous potassium hydroxide solution (0.5 ml) in a small vial. Nickel-aluminum alloy (50 mg) is added, and the mixture is stirred at room temperature. Samples are removed periodically for analysis by gas chromatography.

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[1] Baggiolini, E.G., Lee, H.L., Pizzolato, G., Uskoković, M.R. *J. Am. Chem. Soc.* **1982**, *104*, 6460.

[2] Saavedra, J.E. in: *Umpolung Synthon Chemistry*, Hase, T., Ed., John Wiley and Sons, New York, in press.

[3] Seebach, D., Enders, D. *Angew. Chem.* **1975**, *87*, 1; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15.

[4] Kauffmann, T., Berger, D., Scheerer, B., Woltermann, A. *Chem. Ber.* **1977**, *110*, 3034.

[5] Barton, D.H.R., Lamotte, G., Motherwell, W.B., Narang, S.C. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2030.

[6] Windholz, M., Ed. *The Merck Index*, 10th Edition, Merck and Co., Inc., Rahway, NJ, 1983.

[7] International Agency for Research on Cancer *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 17, Some *N*-Nitroso Compounds, World Health Orgaization, Geneva, 1978.

[8] International Agency for Research on Cancer *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 4, Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents, World Health Organization, Geneva, 1974.

[9] Lunn, G., Sansone, E.B., Keefer, L.K. *Carcinogenesis* **1983**, *4*, 315.

[10] Lunn, G., Sansone, E.B., Keefer, L.K. *Food Cosmet. Toxicol.* **1981**, *19*, 493.

[11] Lunn, G., Sansone, E.B., Keefer, L.K. *Environ. Sci. Technol.* **1983**, *17*, 240.

[12] Schwenk, E., Papa, D., Hankin, H., Ginsberg, H. *Org. Synth. Coll. Vol.* III, 742 (1955).

[13] Williams, H. *J. Org. Chem.* **1964**, *29*, 2046.

[14] Tolf, B.-R., Siddiqui, M.T., Dahlbom, R., Åkeson, Å., Theorell, H. *Eur. J. Med. Chem. Chim. Ther.* **1982**, *17*, 395.

[15] Dewar, M.J.S. in: *Molecular Rearrangements*, de Mayo, P., Ed., Wiley-Interscience, New York, 1963, p. 295.

[16] International Agency for Research on Cancer *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 1, World Health Organization, Geneva, 1972, p. 80.

[17] Billica, H.R., Adkins, H. *Org. Synth. Coll. Vol.* III, 176 (1955).

[18] Sansone, E.B., Lunn, G., Jonas, L.A., Keefer, L.K. in: *N-Nitroso Compounds: Occurrence and Biological Effects*, Bartsch, H., O'Neill, I.K., Castegnaro, M., Okada, M., Eds., World Health Organization (IARC Scientific Publications No. 41), Geneva, 1982, p. 137.

[19] Emmett, G.C., Michejda, C.J., Sansone, E.B., Keefer, L.K. in: *Safe Handling of Chemical Carcinogens, Mutagens, Teratogens and Highly Toxic Substances*, Walters, D.B., Ed., Ann Arbor Science Publishers, Inc., Ann Arbor, MI, 1980, p. 535.

[20] Seebach, D., Wykypiel, W. *Synthesis* **1979**, 423.

[21] Staskun, B., van Es, T. *J. Chem. Soc.* [C] **1966**, 531.

[22] Evdokimoff, V. *Gazz. Chim. Ital.* **1952**, *82*, 315; *C.A.* **1954**, *48*, 636.

[23] Schwenk, E., Papa, D., Whitman, B., Ginsberg, H. *J. Org. Chem.* **1944**, *9*, 1.

[24] Toth, B. *Cancer* **1977**, *40*, 2427.

[25] International Agency for Research on Cancer *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 8. Some Aromatic Azo Compounds, World Health Organization, Geneva, 1975.

[26] Druckrey, H., Lange, A. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **1972**, *31*, 1482.

[27] Leopold, G.H. *Z. Phys. Chem.* **1910**, *71*, 59.

[28] Narbutt, J.v. *Z. Phys. Chem.* **1905**, *53*, 697.

[29] Buckingham, J., Ed. *Dictionary of Organic Compounds*, 5th Edn., Vol. 2, Chapman and Hall, New York, 1982, p. 2058.

[30] Key, A., Dutt, P.K. *J. Chem. Soc.* **1928**, 2035.

[31] Putvinskaya, T.M., Dymchenko, M.M., Starodubtsev, A.M. *Zh. Prikl. Khim.* **1964**, *37*, 2764; *C.A.* **1965**, *62*, 8988g.

[32] Walden, P., Ulich, H., Laun, F. *Z. Phys. Chem.* **1925**, *114*, 275.

[33] Holmes, E.L., Ingold, C.K. *J. Chem. Soc.* **1926**, 1328.