Reduction of Nitrosamines with Aqueous Titanium Trichloride: Convenient Preparation of Aliphatic Hydrazines

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Received February 28, 1984

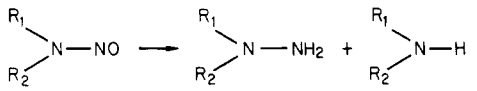
The reduction of selected nitrosamines by aqueous $TiCl_3$ has been investigated. In general, aliphatic nitrosamines were converted in good yield to the corresponding hydrazines, with little overreduction to the amines. Reaction proceeded rapidly at room temperature in both alkaline and acidic media. A variety of *N,N*-dialkylhydrazines have been isolated by using the $TiCl_3$ method, which compares favorably with previously reported procedures for preparatively converting nitrosamines to hydrazines. In the reduction of *N*-nitroso-*N*-methylaniline, the proportion of amine in the product increased significantly as the pH of the reaction mixture was lowered, presumably reflecting the known instability of arylalkylnitrosamines in strong acid, coupled with a ready reducibility of the corresponding Fischer–Hepp intermediates; some tendency toward reductive cleavage of the *N*-aryl-*N*-alkylhydrazine's N–N bond was also noted. Reduction of an α-nitrosamino ether gave the monoalkylhydrazine as the major product, while all other reducing agents studied converted this starting material chiefly to a mixture of primary and secondary amines.

We have been studying the ability of various potential reducing agents to degrade *N*-nitrosodialkylamines and related potent carcinogens by cleaving them quantitatively to the corresponding amines.[1] Titanium trichloride ($TiCl_3$) seemed worthy of attention in this regard; it is commercially available as a stable aqueous solution, and has been shown to serve as a powerful reductant for a wide variety of organic substrates, often under exceptionally mild conditions.[2,3]

Until now, no one appears to have reported the successful reaction of $TiCl_3$ with an *N*-nitroso compound. Nevertheless, there is ample evidence in the literature that N–N bonds can be reductively cleaved by using this reagent. For example, 2,4-dinitrophenylhydrazones were reduced to 1,2,4-triaminobenzene,[4] certain azides were reduced to amines,[5] and N^G-nitroarginyl peptides have been selectively cleaved to the deprotected arginyl peptides.[6] Even the triple bond of dinitrogen has been reductively broken, ammonia being produced in the presence of aqueous $TiCl_3$, hydrogen gas, and suitable transition metal catalysts.[7]

Not all N–N bonds exposed to this reagent have been cleaved, however. Thus, an aliphatic azo dioxy compound produced as an intermediate byproduct in nitroalkane reduction was reduced only to the azoxy alkane at pH 6.[2] In addition, reduction of some aryl azo,[8] diazonium,[9] and hydrazo[10] compounds proceeded no farther than the hydrazine oxidation state, while others were completely cleaved to the corresponding benzidines and aniline derivatives.[10] It is also noteworthy that Ti(II) reagents prepared by reducing $TiCl_4$ converted several nitrosamines

Scheme I



a, nitrosamine b, hydrazine c, amine

1, $R_1 = R_2 =$ Me; 2, $R_1 = R_2 =$ Et; 3, $R_1 = R_2 = n$-Pr; 4, $R_1 = R_2 = i$-Pr; 5, $R_1 = R_2 = n$-Bu; 6, $R_1 + R_2 = (CH_2)_4$; 7, $R_1 + R_2 = (CH_2)_5$; 8, $R_1 + R_2 = (CH_2)_2O(CH_2)_2$; 9, R_1 = Me; R_2 = Ph; 10, R_1 = Me; $R_2 = MeOCH_2$; 11, $R_1 = CD_3$; $R_2 = MeOCH_2$; 12, R_1 = Me; R_2 = H; 13, $R_1 = CD_3$; R_2 = H

Table I. Yields of Hydrazines and Amines Produced on Reduction of Nitrosamines with $TiCl_3$ and Other Aqueous Reagents[a]

	reductant				
nitrosamine reduced	acidic (unbuffered) $TiCl_3$ (pH <1)	$TiCl_3$/NH_4OAc (pH 4.6)	$TiCl_3$/NH_3 (pH 9.4)	Zn/HCl	Al/KOH
1a	85:3	83:0.5	73:3	96:9	82:15
2a	82:14	91:0.4	106:5	83:8	
3a	60:14	82:1	112:3	93:7	
4a	92:9	100:0.6	96:3	78:5	
5a	84:9	77:2	72:2	89:9	77:23
6a	97:4	98:0.1	81:0.2	98:3	87:15
7a	95:2	77:12	100:0.8	79:13	
8a	89:0.1	86:3	95:12	98:8	64:43
9a	7:79	50:23	61:11[b]	23:69	

[a] Values given are product ratios (% yield of hydrazine:% yield of amine) measured by GC 1 h after mixing the nitrosamine at room temperature with excess aqueous $TiCl_3$ at pH <1, in NH_4OAc buffer, and in ammonia solution, respectively, with Zn powder in HCl solution, or with Al foil in aqueous KOH. No unreacted nitrosamine was found in any reaction mixture under these conditions; the detection limits for hydrazines, amines, and nitrosamines were 0.1–1% of the theoretical yields. [b] Yield was determined after 5 min. After 1 h hydrazine yield was 43% and amine yield was 27%.

(1) (a) See Lunn, G.; Sansone, E. B.; Keefer, L. K. *Carcinogenesis* **1983**, *4*, 315 and references therein. (b) Preliminary mention of our findings with $TiCl_3$ was also made: 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; pp 137–149.

(2) Mc Murry, J. E. *Acc. of Chem. Res.* **1974**, *7*, 281.

(3) Ho, T.-L. *Synthesis* **1979**, 1.

(4) Mc Murry, J. E.; Silvestri, M. *J. Org. Chem.* **1975**, *40*, 1502.

(5) Stanovnik, B.; Tišler, M.; Polanc, S.; Gračner, M. *Synthesis* **1978**, 65.

(6) Freidinger, R. M.; Hirschmann, R.; Veber, D. F. *J. Org. Chem.* **1978**, *43*, 4800.

(7) Taqui Khan, M. M.; Martell, A. E. *Inorg. Chem.* **1975**, *14*, 938.

(8) Somei, M.; Kato, K.; Inoue, S. *Chem. Pharm. Bull.* **1980**, *28*, 2515.

(9) Citterio, A.; Ramperti, M.; Vismara, E. *J. Heterocycl. Chem.* **1981**, *18*, 763.

(10) Large, N. R.; Stubbs, F. J.; Hinshelwood, C. *J. Chem. Soc.* **1954**, 2736.

0022-3263/84/1949-3470$01.50/0

and a nitramine in ether or dichloromethane solution to hydrazines, while other Ti(II) and Ti(0) reagents either cleaved the N–N bond to amine or were ineffective.[11]

In this paper, we describe the successful reduction of various nitrosamines to the corresponding hydrazines with aqueous $TiCl_3$. Our results indicate that, while this reducing agent is not suitable for the originally conceived purpose (converting nitrosamines to amines), it may hold considerable value as a reagent for the preparation of hydrazines, including compounds which are useful as propellants, as herbicides, and in cancer research as antineoplastic drugs and as carcinogens.[12]

Results and Discussion

Each of the eight aliphatic nitrosamines we studied (**1a–8a**, Scheme I) was reduced to the corresponding *N,N*-dialkylhydrazine as the major product by using aqueous $TiCl_3$ solution as reductant. Results as determined by direct GC analysis of the reaction mixtures are summarized in Table I. Reduction was quite rapid, usually reaching completion within a few minutes at room temperature, and was effective at every pH studied; thus similar results were obtained at pH 9.4 (in the presence of ammonia[13]), at pH 4.2 (buffered with NaOAc), at pH 4.6 (buffered with NH_4OAc[3]), or in the strongly acidic (pH <1) reductant used as received from the supplier. With few exceptions, amine yields were less than 10% while the hydrazines were produced in yields of more than 70%.

Results obtained for the arylalkylnitrosamine we studied, **9a**, were somewhat different from those described above for the purely aliphatic nitrosamines. As shown in Table I, the hydrazine (**9b**) was only a minor product when **9a** was reduced with unbuffered $TiCl_3$, with *N*-methylaniline, **9c**, being produced in 79% yield. It seemed possible that the N–N cleavage observed in this case might be hydrolytic rather than reductive in nature, because **9a** is less stable than the dialkylnitrosamines under such strongly acidic conditions, readily undergoing the Fischer–Hepp rearrangement and other acid-catalyzed denitrosation[14] reactions. We speculated that the mechanism of **9c** production might involve initial N-protonation of the nitrosamino function, followed by reduction of the nitrosonium ion equivalent thus generated before nitrosation of the para position could occur. To test for this possibility, the reduction was effected by using buffered $TiCl_3$ solutions in which such protolysis should be much less extensive. Consistent with this hypothesis, the hydrazine yields increased dramatically as the pH was raised, the observed yield ratios of hydrazine to amine (**9b**:**9c**) going from 7:79 at pH <1 to 61:11 at pH 9.4. Thus the arylalkylnitrosamine can also be successfully converted to the hydrazine as the major product by using $TiCl_3$, provided that Fischer–Hepp conditions are avoided. It is important to note, however, that the arylhydrazine **9b** was somewhat susceptible to reductive cleavage of its N–N bond by excess $TiCl_3$, even in alkaline solution. Thus the hydrazine:amine yield ratio dropped from 61:11 after 5 min to 43:27 after 1 h at pH 9.4. By contrast, no significant drift in hydrazine:amine ratios was observed in the dialkylhydrazines, indicating that their N–N bonds are stable to $TiCl_3$ reduction.

Table II. Yields of *N,N*-Dialkylhydrazines Isolated After Preparative Scale Reductions of Nitrosamines

product isolated	using $TiCl_3$[a] yield, %	mp, °C	lit. mp, °C	ref	previously reported reductions using $LiAlH_4$ yield, %	ref
1b	70	81–82	81–82	15	78	27
3b	94[b]	*b*			41	18
6b	56	110–111	117–119	29	40	29
7b	71	162–163	159–162	33	76	18
8b	76	165–166	167	32	60–70	28

[a] Yields and melting points given are for the hydrochlorides after recrystallization from ethanol. Reductions were performed with acidic $TiCl_3$ as received from the supplier. [b] Dipropylhydrazine hydrochloride proved to be a low melting solid which could not be properly recrystallized. The yield given is based on the weight of semisolid mass isolated. GC analysis showed it to be 92% pure with the major contaminants being the amine and traces of solvent. The nitrosamine was not found at a detection limit of 0.1%.

For purposes of comparison, the nitrosamines were also reacted with other reducing agents. As shown in Table I, results with Zn/HCl[15] were generally comparable to those with $TiCl_3$, except that the low hydrazine:amine yield ratio (23:69) observed for **9a** in Zn/HCl could not be improved by buffering since the reduction would not occur in basic solution. The Al/KOH system[16] consistently produced a larger proportion of amine than the other reducing agents. For this reason, even though the hydrazine was the major product in all four cases studied (Table I), Al/KOH was judged to be synthetically inferior to the other reducing agents and was not further considered. Several of the nitrosamines were also reduced with $LiAlH_4$, giving authentic samples of the commercially unavailable hydrazines for use as reference standards in the GC analyses; a yield comparison of the $LiAlH_4$ and $TiCl_3$ reductions is given in Table II (see below).

Synthetic Utility. The above product distribution data, as measured by direct GC analysis of the reduction mixtures, suggested that *N,N*-dialkylhydrazines might be usefully prepared by $TiCl_3$ reduction of nitrosamines. This has now been confirmed. As shown in Table II, selected hydrazines have been isolated in 56–94% yield by mixing the nitrosamine with 20% $TiCl_3$ in a molar ratio of 1:4, stirring at room temperature for 1 h, basifying, distilling the contents of the reaction vessel under a stream of nitrogen, adding hydrochloric acid to the distillate, and recrystallizing the resulting hydrochloride.

We believe that $TiCl_3$ reduction holds several potential advantages over established methods for converting nitrosamines to hydrazines. It can be used under both acidic and basic conditions, including near-neutral buffers, while dissolving metal reductions are generally restricted to either acid solution (as with Zn reduction[15]) or strongly alkaline media (e.g., with Al as reductant[16]). Yields of hydrazines isolated in the preparative $TiCl_3$ reductions were comparable to those reported for $LiAlH_4$ (Table II), but the need to use anhydrous solvents and inert atmo-

(11) Entwistle, I. D.; Johnstone, R. A. W.; Wilby, A. H. *Tetrahedron* **1982**, *38*, 419. These authors also report that $TiCl_3$ had no effect on the nitrosamines they studied. Presumably, the conditions they used (solvent, etc.) were quite different from ours, given the striking contrast between their observed lack of reactivity and the facile reductions we observed.

(12) Lunn, G.; Sansone, E. B.; Keefer, L. K. *Environ. Sci. Technol.* **1983**, *17*, 240 and references therein.

(13) Karrer, P.; Yen, Y.; Reichstein, I. *Helv. Chim. Acta* **1930**, *13*, 1308.

(14) Williams, D. L. H. *Tetrahedron* **1975**, *31*, 1343.

(15) Hatt, H. H. In "Organic Syntheses"; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. 2, p 211. We generally used HCl in these reductions, but comparable results were obtained with HOAc under the conditions of Hatt; thus when HOAc was used instead of HCl, **1a** was completely reduced (>99.99%) and gave a **1b**:**1c** ratio of 97:3.

(16) 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; pp 535–553.

spheres[17] was avoided, and $TiCl_3$ did not seem to share the potentially dangerous tendency of $LiAlH_4$ to react suddenly and vigorously with nitrosamines following a prolonged induction period.[18] $TiCl_3$ is a selective reductant, it being possible to reduce reactive groupings in the presence of functionalities, such as the ketone, ketal, nitrile, ester, and carboxylate moieties,[19-21] which can be attacked by the other reductants or by extremes of pH. It is effective in the presence of hydroxylic solvents, including water. It is also especially convenient to use, preparative-scale reactions being easily effected simply by mixing the nitrosamine to be reduced with commercially available aqueous $TiCl_3$ solution; the reagent preparation and purification steps (including, obviously, solvent drying) required for successful use of the Ti(II) reductants[11] and $LiAlH_4$ are not necessary for $TiCl_3$ reductions, nor have we identified a need for the hazard containment procedures required in reactions involving flammable solvents or H_2 gas. **(NOTE, HOWEVER, THAT MOST HYDRAZINES[22] AS WELL AS NITROSAMINES[22,23] ARE POTENT CARCINOGENS AND MUST BE TREATED WITH DUE CAUTION.[1])**

Monoalkylhydrazine Preparation. In our own synthesis program, the first hydrazine we sought to prepare after discovering the potential applicability of $TiCl_3$ reduction to such problems was CD_3NHNH_2 (**13b**), a primary hydrazine. In this case, the synthesis could not be effected by reducing the corresponding *N*-nitroso compound (**13a**), because primary alkylnitrosamines are too unstable to serve as generally useful synthetic intermediates.[24] However, certain α-oxidized dialkylnitrosamines have shown promise as primary nitrosamine equivalents,[25] including the ability to undergo facile H–D exchange in activated positions.

Accordingly, we exposed one of these α-alkoxy nitrosamines, **10a**, to various reducing systems with the aim of determining whether any of them are capable of generating the primary hydrazine or its equivalent in preparatively significant yield. Only one reducing system—$TiCl_3$—gave the hydrazine as the major product. All others produced a mixture of amines ($MeNH_2$ and Me_2NH) as the chief product. Neither **10b** nor **10c** was identified in any of these reactions, but both are presumably unstable toward hydrolysis. More interesting was the degree to which reduction of the C–O bond occurred; Me_2NH was produced to the extent of 25–71% with all reagents except $TiCl_3$, signalling an apparent ability of the nitrosamino-, hydrazino-, and/or amino functions to activate C atoms to which they are attached toward net hydrogenolysis of alkoxy substituents α to them.

Table III. Product Distributions in Reductions of 10a Using Various Reagents[a]

reductant	product: $MeNHNH_2$ (**12b**)	$MeNH_2$ (**12c**)	Me_2NH (**1c**)	MeOH[b]
$TiCl_3$	100	30	ND[c]	110
Zn/HCl	1	28	71	96
Al(Hg)	24	48	40	102
Al/KOH	35	54	25	109
Al_2Ni/KOH	ND[d]	45	44	122

[a] Values are % yields as measured by GC 1–6 h after mixing the nitrosamine at room temperature with excess unbuffered $TiCl_3$ solution, Zn powder in HCl, Al amalgam in water, Al foil in KOH solution, or Al_2Ni alloy powder in aqueous KOH. [b] Yields were calculated on the assumption that 1 mol of **10a** would give 1 mol of MeOH. [c] No **1c** was found at a detection limit of 5%. [d] No **12b** was found at a detection limit of 2%.

The fact that $TiCl_3$ induced no detectable hydrogenolysis of the C–O bond during reduction of **10a** coupled with the high yield of the hydrazine and the known[25] susceptibility of the *N*-methyl group in **10a** to isotopic exchange suggested that a preparative attempt might be fruitful. Accordingly, **10a** was refluxed with NaOD in D_2O for 1 h, stirred when cool with $TiCl_3$, rebasified, and distilled into dilute H_2SO_4 after removing insoluble materials. The hydrazine sulfate was isolated by concentrating the receiver contents. The yield of crude product was only 13%, indicating that the preparation of CD_3NHNH_2 might preferably be effected by using previously described procedures.[26] However, it is conceivable that the yield of the $TiCl_3$ procedure could be improved considerably if the scale were increased, especially if a more efficient method of removing the highly water-soluble hydrazine product from the aqueous reaction mixture could be invoked.

In any event, the desired product, **13b**, was isolated from the $TiCl_3$ reduction of a nitrosamine, and MS showed that the deuterium in the $N-CD_3$ group was retained throughout the procedure. We believe this result confirms the potential utility of $TiCl_3$ in the preparation of hydrazines, including primary hydrazines, by reduction of *N*-nitroso compounds.

Experimental Section

Warning. Most nitrosamines and many hydrazines are potently carcinogenic, and should be handled, stored, and discarded with due respect for their toxic potential.[22,23]

General Methods. Melting points were determined on an Electrothermal melting point apparatus. ^1H NMR spectra were determined on a Perkin-Elmer R12B spectrometer at 60 MHz and ^{13}C NMR spectra were run on a Varian XL-100 spectrometer at 25 MHz. IR spectra were obtained on a Perkin-Elmer 467 grating spectrophotometer using sodium chloride disks and MS data were obtained on a Finnigan 3200 spectrometer fitted with a 6000 data system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reagents. All nitrosamines were generously supplied by Dr. C. J. Michejda and Dr. J. E. Saavedra except **3a**, which was purchased from Sigma. $TiCl_3$ was obtained from Fisher Chemical Co. as the 20% aqueous solution. All amine and hydrazine analytical standards were supplied by Aldrich, except for **2b**, **4b**, and **5b**, which were synthesized by $LiAlH_4$ reduction of the nitrosamines.[18,27-29]

(17) The sensitivity of aqueous $TiCl_3$ solutions to autoxidation has been noted (see, for example: Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry. A Comprehensive Text", 2nd ed.; Interscience Publishers: New York, 1966; p 807) with the admonition to handle and store the reagent under an atmosphere of nitrogen, hydrogen, or argon. In our experience, however, satisfactory yields of hydrazines were obtained without taking any precautions to exclude air from the reduction mixtures. Apparently, reduction of the nitrosamine is much faster than the reaction of $TiCl_3$ with air under the conditions we have used, making the extra effort of controlled atmosphere techniques unnecessary.

(18) Zimmer, H.; Audrieth, L. F.; Zimmer, M.; Rowe, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 790.

(19) Mc Murry, J. E.; Melton, J. *J. Am. Chem. Soc.* **1971**, *93*, 5309.

(20) Mc Murry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.

(21) Blaszczak, L. C.; Mc Murry, J. E. *J. Org. Chem.* **1974**, *39*, 258.

(22) International Agency for Research on Cancer. "IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents"; World Health Organization: Geneva, 1974; Vol. 4.

(23) International Agency for Research On Cancer. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some N-Nitroso Compounds"; World Health Organization: Geneva, 1978; Vol. 17.

(24) Müller, E.; Haiss, H.; Rundel, W. *Chem. Ber.* **1960**, *93*, 1541.

(25) Saavedra, J. E. *J. Org. Chem.* **1983**, *48*, 2388 and references therein.

(26) Sucrow, W.; Lübbe, F.; Fehlauer, A. *Chem. Ber.* **1979**, *112*, 1712.

(27) Schueler, F. W.; Hanna, C. *J. Am. Chem. Soc.* **1951**, *73*, 4996.

(28) Zimmer, H.; Audrieth, L. F.; Zimmer, M. *Chem. Ber.* **1956**, *89*, 1116.

Reduction of Nitrosamines–Product Distribution Studies. The nitrosamine to be reduced was dissolved in water or methanol (ca. 5 mg in 500 μL). For reduction by acidic $TiCl_3$, the nitrosamine solution was mixed with 500 μL of reductant solution as received from the supplier, stirred for 1 h, cooled in ice, basified by cautious addition of 1 mL of ice cold 10 M KOH, centrifuged, decanted, and analyzed by GC. The buffered reactions were performed by using a rather more concentrated nitrosamine solution (ca. 17 mg in 500 μL of water) which was mixed with 4 M ammonium (or sodium) acetate solution (1 mL) and titanium trichloride solution (0.5 mL); after 1 h the reaction was cooled in ice, basified with 1 mL of ice cold 10 M KOH solution, centrifuged, decanted, and analyzed by GC. For reduction by alkaline $TiCl_3$, ammonia was used to basify the reaction mixture, the nitrosamine (ca. 18 mg in 2.5 mL of water) being mixed with 0.5 mL of ammonia solution (ca. 29%) and 0.5 mL of titanium trichloride solution; the reaction mixture was analyzed by GC 5 min or 1 h later. For Zn/HCl reduction, the nitrosamine solution was mixed with 500 μL of 1 M HCl and 50 mg of zinc dust, stirred for 24 h, basified with 10 M KOH, and analyzed by GC. For reduction with Al/KOH (or Al_2Ni/KOH), the nitrosamine solution was mixed with 500 μL of 1 M KOH and 22 mg of aluminum foil cut into pieces 2 mm square (or 50 mg of aluminum–nickel alloy powder), stirred for 24 h, decanted, and analyzed by GC. For reduction by Al(Hg),[30] the nitrosamine solution was mixed with an equal volume of water and added to 22 mg of aluminum foil which had been dipped in 2% $HgCl_2$ solution and cut into pieces 2 mm square; the reaction mixture was stirred for 24 h and analyzed by GC. When the procedure of Hatt[15] was adapted, zinc (0.65 g) was added to *N*-nitrosodimethylamine (200 mg) in water (3 mL) and acetic acid (1 mL), stirred at room temperature for 2 h and then at 55–65 °C for 1 h, cooled in ice, basified with 1 mL of ice cold 10 M KOH, and analyzed by GC. In all cases, analyses were performed by direct injection onto a 1.8 m × 2 mm inner diameter silanized glass column in a Hewlett-Packard 5830A gas chromatograph with flame ionization detector and automatic peak area integrator.[1] Injection temperature was 200 °C and the N_2 carrier gas flow rate was about 30 mL/min. Column packings were either 10% Carbowax 20 M plus 2% KOH on 80/100 Chromosorb WAW or 2% Carbowax 20 M plus 1% KOH on 80/100 Supelcoport. The quantity of unreacted nitrosamine as well as of each product was determined by comparing its peak area with that of a known concentration of an alcohol having a convenient retention time which was added to the initial reaction mixture as an internal standard. It was subsequently noted that analytical recoveries of the internal standard were less than 100% in the acidic $TiCl_3$ reaction mixtures (but not in NH_3 buffered solutions), presumably because of alcohol–metal complexation. Control experiments established how much alcohol was lost in this manner and the results in Table I have been corrected accordingly. This led to some variability (e.g., apparent yields exceeding 100%), but the hydrazine:amine ratios shown in Table I appeared to be representative.

Reduction of Nitrosamines–Preparative Scale Reactions. A typical procedure is as follows: **8a** (5.32 g, 46 mmol) was dissolved in water (70 mL) and titanium trichloride solution (20%, 145 mL, 188 mmol) was added. The mixture was stirred at room temperature for 1 h and cooled in ice; solid potassium hydroxide (100 g) was added slowly. After the addition was complete the mixture was allowed to stand for 1 h at room temperature and then it was distilled to dryness under a stream of nitrogen. (Distillation under N_2 was employed[31] to minimize the chance of oxidizing hydrazine product.) The nitrogen entered at the top of the still head and left at the receiver adapter. The nitrogen was bubbled through water (100 mL) as a further trap. When the distillation was complete the flask was allowed to cool; more water (500 mL) was added and the distillation was continued. All distillates and the trap contents were combined, acidified with dilute hydrochloric acid, and evaporated to give crude hydrochloride as a white solid. Recrystallization from ethanol gave the hydrochloride of **8b** (4.80 g, 76%), mp 165–166 °C (lit.[32] mp 167 °C). A second crop (0.2 g, 3%), mp 164–165 °C, was also obtained. The free base could be obtained by basification with 10 M KOH and extraction into ether: IR 3300, 3150, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6 (t, J = 5 Hz, 4 H), 3.2 (broad s, 2 H), 3.7 (t, J = 5 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 66.5, 57.9; MS of the hydrochloride, m/e (%) 102 (M^+, 39), 101 (3), 86 (10), 72 (7), 57 (6), 56 (4), 45 (4), 40 (100).

Anal. Calcd for the hydrochloride $C_4H_{11}ClN_2O$: C, 34.67; H, 8.00; N, 20.21. Found: C, 34.97; H, 8.12; N, 20.27.

The procedures used to prepare the other hydrazines were identical except that **3a** and **5a** were dissolved in methanol rather than water, and the second distillation to dryness was not necessary for any of the other compounds. The hydrazines were identified by MS and by comparison of their hydrochloride melting points with literature values, except for di-*n*-propylhydrazine hydrochloride which was identified by spectral methods: MS, m/e (%) 116 (22), 88 (6), 87 (100), 86 (2), 70 (2), 59 (6), 58 (4), 56 (4), 46 (83); ^1H NMR ($NaOD/D_2O$) δ 0.85 (t, J = 8 Hz, 3 H), 1.5 (m, 2 H), 2.5 (t, J = 8 Hz, 2 H); IR (free base) 3300, 3150, 1580 cm^{-1}.

Methyl-d_3-hydrazine Sulfate. **10a** (2.22 g) was dissolved in 28 mL of 1 M NaOD in D_2O and refluxed under N_2 for 1 h.[25] The reaction mixture was cooled on ice, added to 75 mL of 20% $TiCl_3$, stirred for 1 h, basified with 75 mL of 10 M KOH, centrifuged in convenient portions to remove the opaque blue material, and decanted. The insoluble blue material was stirred with more water and centrifuged again. All portions of clear liquid were combined and distilled under a stream of nitrogen, and the distillate was acidified with dilute H_2SO_4. Evaporation gave an orange oil which crystallized on treatment with ethanol. Crude methyl-d_3-hydrazine sulfate was obtained as white crystals, mp 120 °C, in 13% yield (400 mg). Recrystallization from ethanol gave white crystals, mp 140–141 °C (lit.[31] mp 142 °C). An aliquot of the purified material was dissolved in excess KOH solution and subjected to GC/MS, m/e (%) 45 (6), 46 (8), 47 (55), 48 (14), 49 (100), 50 (2). GC/MS of undeuterated CH_3NHNH_2 under these conditions, m/e (%) 44 (7), 45 (72), 46 (100), 47 (4), 48 (0), 49 (3).

Acknowledgment. We thank Drs. C. J. Michejda and J. E. Saavedra for the gift of many nitrosamine standards and Mary Shorter for GC/MS analysis. Research was sponsored in part by the National Cancer Institute under Contract No. N01-C0-23910 with Program Resources, Inc.

Registry No. **1a**, 62-75-9; **1b**, 57-14-7; **2a**, 55-18-5; **2b**, 616-40-0; **3a**, 621-64-7; **3b**, 4986-50-9; **4a**, 601-77-4; **4b**, 921-14-2; **4b**·HCl, 90889-75-1; **5a**, 924-16-3; **5b**, 7422-80-2; **6a**, 930-55-2; **6b**, 16596-41-1; **7a**, 100-75-4; **7b**, 2213-43-6; **8a**, 59-89-2; **8b**, 4319-49-7; **8b**·HCl, 62551-70-6; **9a**, 614-00-6; **9c**, 100-61-8; **10a**, 39885-14-8; **13b**·H_2SO_4, 70609-01-7; $TiCl_3$, 7705-07-9.

(29) Wright, J. B.; Willette, R. E. *J. Med. Pharm. Chem.* **1962**, *5*, 815.
(30) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639.
(31) Audrieth, L. F.; Diamond, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 4869.
(32) Diamond, L. H.; Audrieth, L. F. *J. Am. Chem. Soc.* **1955**, *77*, 3131.
(33) Omietanski, G. M.; Kelmers, A. D.; Shellman, R. W.; Sisler, H. H. *J. Am. Chem. Soc.* **1956**, *78*, 3874.