

## Nitrosamines from Tertiary Amines and Dinitrogen Tetraoxide

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A preparative nitrosolysis of aliphatic acyclic and cyclic tertiary monoamines to nitrosamines was brought about by treatment with dinitrogen tetraoxide in carbon tetrachloride at 0–45 °C. Dealkylation was restricted, where applicable, to demethylation. Competitive oxidation to an amide was observed in the formation of dibutylformamide from tributylamine. Diamine dinitrate salts, without nitrosamine formation, were obtained from 1,4-dimethylpiperazine and 1,4-diaza[2.2.2]bicyclo-octane; however, each dinitrate salt thermolysed at 180–200 °C to give a small amount of 1,4-dinitrosopiperazine. In acetic anhydride dinitrogen tetraoxide converted amines less efficiently, gave lower yields of nitrosamines, was less selective in dealkylation, and introduced the formation of by-products.

Both nitrosolyses to give nitramines and nitrosolyses to give nitrosamines from aliphatic tertiary monoamines have been erratic and often inefficient. To fulfil a need for the preparative conversion of trialkyl amines into nitramines<sup>1</sup> a search for a reagent as an alternative to nitrous acid to give an improved nitrosolysis was undertaken. For the subsequent conversion of a nitrosamine to a nitramine efficient oxidations are known.<sup>2</sup>

Over 50 trialkyl and arylalkyl tertiary monoamines showing a wide variety of structures have been investigated for nitrosolysis by nitrous acid. Under optimal conditions the amines RR<sup>1</sup>NCHR<sup>2</sup>R<sup>3</sup> and nitrous acid (4 to 10 molar ratio) in acetic acid (adjusted to pH 3.7 to 5) at 90 °C for 3 to 16 h gave nitrosamines RR<sup>1</sup>NNO (7–70%) and carbonyl compounds R<sup>2</sup>R<sup>3</sup>CO (up to 80%), often with low conversion of the amine.<sup>3–6</sup> A reaction between tributylamine and nitrous acid gave dibutyl-nitrosamine (6%), butyraldehyde (7%), dibutylamine (2%), an unsaturated tertiary amine, three amino alcohols, and an amino ketone.<sup>4</sup>

Unstable complexes between a tertiary amine and dinitrogen tetraoxide were formulated as R<sub>3</sub>N<sup>+</sup>NO<sup>-</sup>ONO<sub>2</sub> and R<sub>3</sub>N-nN<sub>2</sub>O<sub>4</sub> (n ≥ 1).<sup>7–10</sup> Transnitrosation from triethylnitrosoammonium nitrate was proposed to account for *N*-nitrosation of a secondary amine in the presence of triethylamine and dinitrogen tetraoxide in an inert solvent at –60 to 20 °C. Triethylamine was recovered.<sup>11</sup>

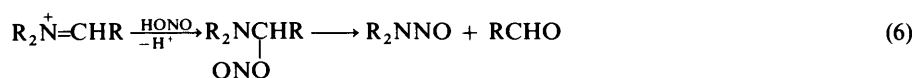
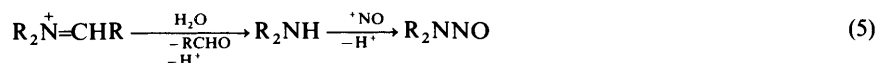
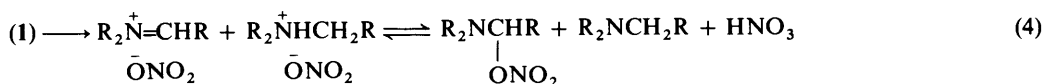
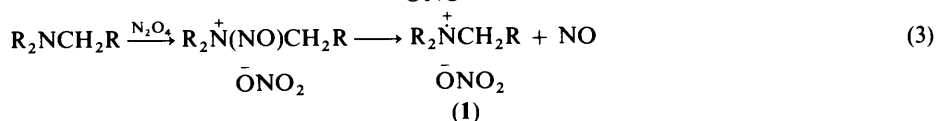
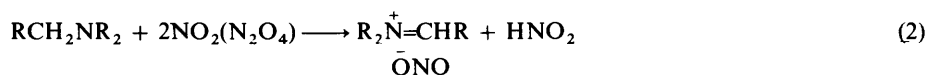
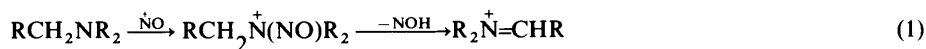
There is only one report of nitrosolytic dealkylation of tertiary amines by treatment with dinitrogen tetraoxide. *N,N*-Dimethylaniline and its 4-nitro and 2,4-dinitro derivatives in carbon tetrachloride were converted into *N*-methyl-*N*-nitroso-

2,4-dinitroaniline; ring nitration and nitrosolysis also occurred with the 4,*N,N*-trimethylaniline but the 2,4,6-trimethyl and the 2,4,6-trichloro derivatives of *N,N*-dimethylaniline underwent nitrosolysis only and *N,N*-dimethylpicramide and benzyl-trimethylammonium chloride were each unreactive.<sup>12</sup>

Explanations for nitrosolyses of tertiary amines by nitrous acid correlated structural effects and kinetic results in mechanism variations which held in common an iminium cation, R<sub>2</sub>N<sup>+</sup>=CR<sub>2</sub>, as a key intermediate.<sup>3–6</sup> It was presumably formed by an elimination of nitroxyl from a nitrosoammonium cation, produced from the amine and the nitrosonium cation, equation (1).<sup>3</sup>

An alternative source of the iminium cation intermediate was proposed for the very poor conversions of tertiary aliphatic amines in mixtures of nitric and acetic acids in acetic anhydride into formamides, acetamides, and nitrosamines. It involved α-oxidation initiated by radical α-hydrogen abstraction by nitrogen dioxide generated *in situ*, equation (2).<sup>13</sup> This α-oxidation was not, however, differentiated from α-hydrogen transfer from an aminium cation radical provided for by either an electron transfer from the tertiary amine<sup>14</sup> or by homolytic dissociation of a nitrosoammonium cation, equations (3) and (4).<sup>15</sup> Since amine radical cations abstract hydrogen from CH bonds to form ammonium cations, equation (4),<sup>14</sup> presumptive evidence for the presence of a dimethylaniline radical cation, from the amine and dinitrogen tetraoxide, is now found in the formation of the nitrated nitrosamine (4).

The conversion of an iminium cation intermediate into a nitrosamine and a carbonyl compound has been accounted for





for the nitrosamines (10) and (11) (Table)]. A reported<sup>13</sup> promotion of nitrosamine formation from the tertiary amines (2) and (3) by the presence of hydrochloric acid in reactions brought about by treatment with nitric and acetic acids in acetic anhydride under conditions whereby nitrogen dioxide was produced *in situ* was found to be incorrect for the amine (2) and marginally effective for the amine (3).<sup>18</sup> An absence of nitramine formation was evidence for an absence of the formation of a secondary amine as an intermediate insofar as the chloride anion was known to be an effective catalyst for the nitration of a secondary amine to a nitramine.<sup>17</sup>

The addition of dinitrogen tetroxide to a tertiary amine, *e.g.* (3) or (7) in dimethyl sulphoxide (DMSO) at  $-20^{\circ}\text{C}$  brought about a violent reaction with spontaneous combustion. Although the reaction was moderated by diluting dinitrogen tetroxide with DMSO the system was not investigated further since the efficiency of nitrosamine formation was low.

Dinitrogen tetroxide and nitrous acid were further compared in the nitrosolysis of the amines (4) and (5). Under the recommended optimal conditions<sup>3</sup> nitrous acid afforded the nitrosamines (10) (68%) and (11) (82%) with recovery of the amines (4) (41%) and (5) (50%). A complete conversion of the amine (5) was achieved with a 30 molar ratio of nitrous acid but gave a slightly lower yield (74%) of the nitrosamine (11). As shown in the Table, nitrosolysis by dinitrogen tetroxide completely converted these and other amines into nitrosamines in high yields. In further contrast with the results afforded by nitrous acid,<sup>4</sup> a minimum of co-products from oxidation in an alkyl group in the reactions with dinitrogen tetroxide is advantageous.

To account for the sole example of the detection of an amide from a tertiary amine and dinitrogen tetroxide in carbon tetrachloride the formation of dibutylformamide (14) (40%), was attributed to an  $\alpha$ -oxidation.<sup>13</sup> The lack of detectable formation of formamides and/or other oxidation products in the similar reactions with amines (2), (4)—(7) was unexpected.

The formation of the dinitrate salts (15)·2HNO<sub>3</sub> and (16)·2HNO<sub>3</sub> from the diamines and dinitrogen tetroxide in carbon tetrachloride was seen as another example of hydrogen abstraction from CH bonds by an amine radical cation [equation (4)]. In these examples  $\alpha$ -hydrogen transfer to leave an iminium cation [equation (4)], was not detected.

Certain observations need further clarification. There was unexpectedly an absence of aromatic ring nitration during the nitrosolysis of the amines (4) and (5) with dinitrogen tetroxide in carbon tetrachloride to the nitrosamines (10) and (11). In contrast, a similar treatment of dimethylaniline gave *N*-methyl-*N*-nitroso-2,4-dinitroaniline (62%).<sup>12,19,\*</sup>

Nitrosolysis with dinitrogen tetroxide occurred with a strong but unaccounted for predominance of demethylation over alternative dealkylation to give the nitrosamines (10)—(13). A similar result was encountered in the nitrosolysis of these and other tertiary amines by nitrous acid.<sup>3-6</sup>

Apparently the formation of 1-nitrosopiperidine (13) (82%) in greater efficiency than was observed for 1-nitrosopyrrolidine (12) (42%) revealed a ring-size effect. A similar effect was previously noted.<sup>5b</sup>

## Experimental

**CAUTION.** Nitrosoamines may be carcinogenic.

Instruments included Pye-Unicam SP-200 i.r., Varian A-60 and T-60 n.m.r. spectrometers. Elemental analyses were pro-

vided by Mico-Tech Laboratory, Skokie, Illinois. Product identifications and yields were determined by g.c. analysis by comparison with values obtained for the known compounds and were obtained from a HP-5790 instrument with a HP-3390A integrator (column: 3% OV-17 on 80/100 Gas. Chrom Q, stainless steel 6 ft  $\times$   $\frac{1}{8}$  in; carrier gas nitrogen; column temp. between 110 and 150  $^{\circ}\text{C}$ , with FID).

The amines (2)—(4), (6), (7), (15), (16), and (19) and Eschenmoser's salt were commercially available. *N,N*-Dimethyl- $\beta$ -phenethylamine (5) was prepared from  $\beta$ -phenethylamine and formaldehyde.<sup>20</sup> The nitrosamines (8)—(13) were prepared by published procedures (Table). Dinitrogen tetroxide (99.5%) was obtained from Matheson Chemical Co. and used without further purification except where noted otherwise. Dimethylnitrosamine and dimethylnitrosoamine were obtained from dimethylcarbonyl chloride and silver nitrate.<sup>21</sup>

**General Procedure.**—Dinitrogen tetroxide (excess) was added to a stirred solution of a tertiary amine (15 mmol) in carbon tetrachloride (15 ml) precooled to 0  $^{\circ}\text{C}$ . During the addition the temperature rose to 40—50  $^{\circ}\text{C}$ . The mixture was cooled to 25  $^{\circ}\text{C}$ , stirred for 14 h, treated with water (50 ml), and extracted with ether (3  $\times$  100 ml) to give the nitrosamine (Table).

From the tributylamine (3) a mixture of di-*n*-butylformamide (14) and dibutylnitrosoamine (9) was isolated after removal of ether and co-distilled at 62—64  $^{\circ}\text{C}$  (0.2 mmHg).<sup>22</sup> The distillate was shown by g.c. analysis to contain the amide (14) (40% yield) and the nitrosamine (42% yield).

The mixture of 1,4-dimethylpiperazine (15) (1.71 g, 150 mmol) and an excess of dinitrogen tetroxide in carbon tetrachloride (15 ml) at 0  $^{\circ}\text{C}$  gave an immediate precipitation of the diamine dinitrate, (15)·(HNO<sub>3</sub>)<sub>2</sub>. The slightly hygroscopic salt was filtered off, dried *in vacuo* for 6 h, and recrystallized from ethanol (1.23 g, 35%), m.p. 212—214  $^{\circ}\text{C}$  (decomp.) (Found: C, 29.55; H, 6.9; N, 23.50. Calc. for C<sub>6</sub>H<sub>16</sub>N<sub>4</sub>O<sub>6</sub>: C, 30.00; H, 6.71; N, 23.32%). The same diamine dinitrate was quantitatively obtained from the diamine (15) (150 mmol) and nitric acid (100%; 2 ml) in dry ether (30 ml) at 0  $^{\circ}\text{C}$ .

Similar treatment of 1,4-diaza[2.2.2]bicyclo-octane (16) (*a*) with dinitrogen tetroxide in carbon tetrachloride gave the diamine dinitrate (16)·(HNO<sub>3</sub>)<sub>2</sub> (74%), m.p. 185—186  $^{\circ}\text{C}$  (decomp.) after recrystallization from ethanol and (*b*) with nitric acid (100%) in ether gave the dinitrate salt quantitatively (Found: C, 30.15; H, 5.95; N, 23.45. Calc. for C<sub>6</sub>H<sub>14</sub>N<sub>4</sub>O<sub>6</sub>: C, 30.25; H, 5.92; N, 23.52%).

When the diamine (15) (150 mmol) and an excess of dinitrogen tetroxide were mixed at 15 to 20  $^{\circ}\text{C}$  (no solvent) a violent reaction occurred with flames, evolution of brown fumes, and formation of intractable tar.

Thermolysis of each salt (15)·(HNO<sub>3</sub>)<sub>2</sub> and (16)·(HNO<sub>3</sub>)<sub>2</sub> (150 mmol) in a small flask heated to 180—200  $^{\circ}\text{C}$  brought about a copious evolution of brown fumes and formation of a tarry residue. A chloroform extract from the residue gave an i.r. spectrum that was superimposable throughout with an authentic spectrum obtained for 1,4-dinitrosopiperazine (17) prepared from piperazine and nitrous acid.<sup>23</sup>

To achieve rigorous exclusion of moisture in one experiment glassware was baked at 90  $^{\circ}\text{C}$  for 14 h prior to use, dinitrogen tetroxide was passed through phosphorus pentoxide before it entered the reaction vessel, a tube of anhydrous calcium chloride protected the system from atmospheric moisture, carbon tetrachloride and dimethylbenzylamine (4) were both anhydrous, and the system was flushed with nitrogen after its passage through Drierite. Water was not added during work-up; instead the excess of dinitrogen tetroxide and other nitrogen oxides (if present) were removed under reduced pressure. Gas chromatographic analysis of the residue showed

\* Nitric acid (*d* 1.5) at  $-10$  to 0  $^{\circ}\text{C}$  converted (90%) the amine (4) into its *m*-nitro derivative (54% yield) and converted (90%) the amine (5) into its *p*-nitro derivative (78% yield).<sup>19</sup>

the presence of the nitrosamine (10) (91%); no other material was detected.

*Acetic Anhydride as Solvent.*—A mixture of dinitrogen tetraoxide (excess) and *N,N*-dimethylbenzylamine (4) (15 mmol) in acetic anhydride (150 mmol), prepared at  $-5^{\circ}\text{C}$  and stirred at  $25^{\circ}\text{C}$  for 14 h, gave the nitrosamine (10) (65%), a trace amount of amides (i.r. 1 635 and 1 705  $\text{cm}^{-1}$ ), and recovered amine (4) (42%). G.c. failed to detect benzaldehyde ( $10^{-7}$  mol would have been noted). Similar reactions with the amines (2), (3), (5–7), and (19) were carried out (Table).

A mixture of dinitrogen tetraoxide (excess), *N,N*-dimethylbenzylamine (4) (15 mmol), concentrated hydrochloric acid (5 mmol), and acetic anhydride (150 mmol), prepared at  $-5^{\circ}\text{C}$  and stirred at  $25^{\circ}\text{C}$  for 14 h, gave the nitrosamine (10) (87%), trace amounts of amides (i.r. 1 635, 1 705, and 1 760  $\text{cm}^{-1}$ ), and recovered amine (4) (19%). G.c. did not detect benzaldehyde. Similar reactions with amines (2), (3), (5–7), and (19) were carried out (Table).

*Nitrous Acid Reactions.*—A solution of *N,N*-dimethylbenzylamine (4) (2.7 g, 0.02 mol) in acetic acid (60%; 100 ml) buffered to pH 4–5 with sodium acetate (13.6 g) was stirred and heated. Sodium nitrite (13.8 g, 0.2 mol) in water (50 ml) was added slowly (45 min) and the mixture was stirred at  $90^{\circ}\text{C}$  for 2 h. It was cooled, diluted with water (50 ml), and extracted with ether ( $3 \times 100$  ml). The ether extract was washed with aqueous potassium carbonate (10%) until the aqueous layer was basic and then with saturated brine; it was then dried ( $\text{MgSO}_4$ ). Removal of the solvent left benzylmethylnitrosoamine (10) (1.20 g, 68%) as a yellow oil. The aqueous layer was made basic with potassium hydroxide and extracted with ether to give recovered dimethylbenzylamine (1.12 g, 41%).

A similar reaction with *N,N*-dimethyl- $\beta$ -phenethylamine (5) gave the nitrosamine (11) [82% based on 50% recovery of the amine (5)].

*Nitrate and Nitrite Esters from Eschenmoser's Salt.*—Equimolar portions (5 mmol) of Eschenmoser's salt [ $(\text{Me}_2\text{N}^+\text{CH}_2)\text{I}^-$ ,  $\delta(\text{CF}_3\text{CO}_2\text{H})$  3.16 (s, 6 H) and 6.46 (br s, 2 H)] and silver nitrite in acetonitrile (10 ml) was stirred at  $25^{\circ}\text{C}$  for 16 h. Precipitation of silver iodide was noted after 5 min and a quantitative yield was obtained. Dimethylnitrosoamine was detected after 10 min and identified by t.l.c. comparison with an authentic sample. In similar experiments Eschenmoser's salt failed to react with silver nitrate in acetonitrile at  $25^{\circ}\text{C}$  for 5 days; however, in dry THF (10 ml) at  $25^{\circ}\text{C}$  for 16 h reaction gave a mixture of the hemiaminal nitrate ester ( $\text{Me}_2\text{N}^+\text{CH}_2\text{NO}_3 \longleftrightarrow \text{Me}_2\text{NCH}_2\text{ONO}_2$ ),  $\delta(\text{CF}_3\text{CO}_2\text{H})$  3.36 (s, 6 H) and 7.50 (br s, 2 H), and silver

iodide (quantitative). Dimethylnitrosoamine was not detected by either t.l.c. or n.m.r.; the authentic nitramine gave  $\delta(\text{CF}_3\text{CO}_2\text{H})$  3.40 (s).

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