Nitrosolysis of Tertiary Amines: Piperidines, Piperazines, Bisdimethylamino-alkanes, and Functionalized Methyldialkylamines

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Preparative amounts of mono- and di-nitrosamines were obtained from aliphatic cyclic and acyclic tertiary monamines and diamines by treatment with dinitrogen tetraoxide in carbon tetrachloride at 0—45 °C. *N*-Methyl- and *N*-ethyl-piperidines (**1**) and (**2**) gave *N*-nitrosopiperidine (**15**), but *N*-isopropyl- and *N*-t-butyl-piperidines (**3**) and (**4**) did not. *N*-Methyl-, *N*-ethyl-, *N*-isopropyl- and *N*-t-butyl-*N'*-methylpiperazines (**5**)—(**8**) gave *N,N'*-dinitrosopiperazine (**22**) (in 90%, 81%, 55%, and 8% yields, respectively) and the diamine (**8**) also gave *N*-t-butyl-*N'*-nitrosopiperazine (**23**) (45%). The *N'*-nitroso and the *N'*-nitro derivatives of *N*-methylpiperazine were similarly converted into *N,N'*-dinitroso- and *N*-nitroso-*N'*-nitropiperazines (**22**) (45%) and (**30**) (53%). Bisdimethylaminoalkanes $(Me_2N)_2(CH_2)_n$ (**10**)—(**14**) gave bismethylnitrosaminoalkanes $[MeN(NO)]_2(CH_2)_n$ (**24**)—(**27**) and dimethylnitrosamine (**28**): n = 1(0%,90%); n = 2(68%,0%); n = 3(48%,43%); n = 4(41%,38%); n = 6(58%,35%). β-Dimethylaminopropionitrile (**18**), 1-methylnitrosamino-2-dimethylaminoethane (**17**), and α-dimethylaminoacetic acid (**19**) gave the corresponding nitrosoamines by replacement of an *N*-methyl group.

In earlier reports, nitrosamines were obtained from cyclic and acyclic tertiary amines which contained α-hydrogen on treatment with dinitrogen tetraoxide in carbon tetrachloride at 0—45 °C. Where competition existed, dealkylation was predominantly demethylation. The following steps [equation (1)] were proposed to account for this nitrosolysis.[1,2]

$$R_2NCH_2R \xrightarrow[-\bar{O}NO_2]{N_2O_4} R_2\overset{+}{N}(NO)CH_2R \xrightarrow{-NO} \underset{a}{R_2\overset{+\cdot}{N}CH_2R}$$

$$2a \longrightarrow \underset{b}{R_2\overset{+}{N}{=}CHR} + R_2\overset{+}{N}HCH_2R \left[\begin{array}{l} \xrightarrow{-H^+} R_2NCH_2R \text{ for recycle} \\ \xrightarrow{\bar{O}NO_2} R_2\overset{+}{N}HCH_2R\ \bar{N}O_2 \text{ sometimes insoluble} \end{array} \right]$$

$$\bar{O}NO_2 + N_2O_4 \rightleftharpoons \bar{O}NO + N_2O_5$$

$$b \xrightarrow{\bar{O}NO} R_2N\underset{\displaystyle ONO}{\underset{|}{C}}HR \longrightarrow R_2NNO + RCHO \qquad (1)$$

Heterolytic dissociation of an intermediate nitrosammonium cation, enhanced by the greater stability of certain carbonium ions thus formed, was proposed to account for certain nitrosamine formations which did not involve α-hydrogen expulsion and co-formation of a carbonyl compound [equations (2) and (3)].[3,4]

$$R'_2NCR_3 \xrightarrow{NO^+} R_2N(NO)CR_3 \longrightarrow R_2NNO + R_3C^+ \qquad (2)$$

$$(R_2N)_2CH_2 \xrightarrow{NO^+} R_2\overset{+}{N}(NO)CH_2NR_2 \longrightarrow R_2NNO + R_2\overset{+}{N}CH_2 \qquad (3)$$

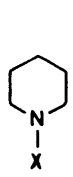
We now report investigations into the *N*-methyl-, *N*-ethyl-, *N*-isopropyl-, and *N*-t-butyl-piperidines (**1**)—(**4**); the corresponding *N*-alkyl-*N'*-methylpiperazines (**5**)—(**8**) and 1,4-diazabicyclo-octane (**9**) (Dabco); the five bisdimethylaminoalkanes (**10**)—(**14**); and the five methyldialkylamines (**17**)—(**21**), each also containing an additional functional group.

Results

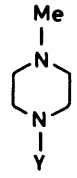
Piperidines.—Dinitrogen tetraoxide in carbon tetrachloride at 0—45 °C converted the *N*-methyl- and *N*-ethyl-piperidines (**1**) and (**2**) into the *N*-nitrosopiperidine (**15**) (80 and 72%), but failed to bring about similar conversions of the *N*-isopropyl- and *N*-t-butyl-piperidines (**3**) and (**4**) which were recovered unchanged (60 and 45%). Nitrosonium tetrafluoroborate also failed to replace the *N*-t-butyl group in the amine (**4**) with a nitroso group, and both nitronium tetrafluoroborate and nitric acid (90%) in concentrated sulphuric acid failed to convert the amine (**4**) into the nitramine (**16**).

Piperazines.—Similar treatment with dinitrogen tetraoxide converted Dabco (**9**) into its dinitrate salt (70%) [*cf.* equation (1)] and 1,4-dinitrosopiperazine (**22**) (15%), and the *N*-methyl-, *N*-ethyl-, *N*-isopropyl-, and *N*-t-butyl-*N'*-methyl-piperazines (**5**)—(**8**) into the same dinitrosamine (**22**) (90, 81, 55, and 8%). The latter amine (**8**) also gave the mononitrate salt (45%) of *N*-t-butyl-*N'*-nitrosopiperazine, (**23**).

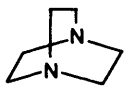
Dimethylaminoalkanes.—Of the five bis-dimethylamino-alkanes (**10**)—(**14**), the latter four gave the bis-methylnitros-aminoalkanes (**24**)—(**27**) (41—68%) by replacement of methyl groups during nitrosolysis with dinitrogen tetraoxide, and four of the amines, (**10**) and (**12**)—(**14**), gave dimethylnitrosamine



(1)-(4),(15),(16)



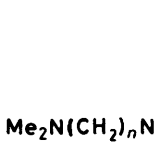
(5)-(8),(20),(21)

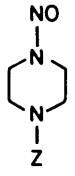


(9)

(1) X = Me
(2) X = Et
(3) X = Me_2CH
(4) X = Me_3C
(15) X = NO
(16) X = NO_2

(5) Y = Me
(6) Y = Et
(7) Y = Me_2CH
(8) Y = Me_3C
(20) Y = NO
(21) Y = NO_2

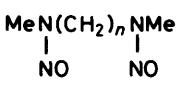


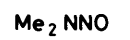


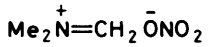
(10) n = 1
(11) n = 2
(12) n = 3
(13) n = 4
(14) n = 6

(17) Z = $CH_2N(NO)Me$
(18) Z = CH_2CN
(19) Z = CO_2H

(22) Z = NO
(23) Z = Me_3C
(30) Z = NO_2



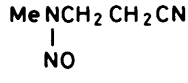


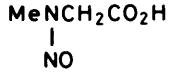


(24) n = 2
(25) n = 3
(26) n = 4
(27) n = 6

(28)

(29)





(31)

(32)

(28) (35—90%) by replacement of methylene derivatives. When the reaction with bis(dimethylamino)methane (**10**) at −20 °C was interrupted after 15 min the only product isolated was dimethylmethyleneammonium nitrate (**29**), identified by comparison with an authentic sample prepared from Eschenmoser's salt $[Me_2N{=}CH_2]^+I^-$ and silver nitrate.

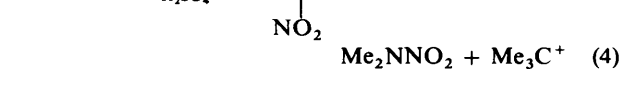
Functionalized Methyldialkylamines.—In comparison with the conversions (**5**)→(**22**) and (**11**)→(**24**), a β-nitrosamino group decreased the extent of conversion of *N*-methyl-*N'*-nitrosopiperazine (**20**) into the dinitrosamine (**22**) (45%), and that of 1-dimethylamino-2-methylnitrosaminoethane (**17**) into the dinitrosamine (**24**) (48%). Similarly, *N*-methyl-*N'*-nitropiperazine (**21**) gave *N*-nitroso-*N'*nitropiperazine (**30**) (53%).

β-Dimethylaminopropionitrile (**18**) efficiently gave β-methylnitrosaminopropionitrile (**31**) (78%), and α-dimethylaminoacetic acid (**19**) gave α-methylnitrosaminoacetic acid (**32**) (24%).

Discussion

Key steps in an explanation for the formation of nitrosamines and aldehydes from reactions between certain tertiary aliphatic amines and dinitrogen tetraoxide required both the expulsion of an α-hydrogen and nitric oxide from a trialkylnitrosoammonium cation and the dissociation of a hemiaminalnitrite ester [equation (1)].

Results obtained from the *N*-alkylpiperidines (**1**)—(**4**) and the *N,N'*-dialkylpiperazines (**5**)—(**9**) showed that primary alkyl groups tended to be replaced easily by the nitroso group, the isopropyl group was less readily replaced, and the t-butyl group was replaced in low yield or not at all. Since replacement of a t-butyl group cannot proceed according to the process described in equation (1), it was assumed that a heterolytic dissociation of a nitrosammonium cation partially accounted for the formation of *N,N'*-dinitrosopiperazine (**20**) (8%) from *N*-t-butyl-*N'*-methylpiperazine (**5**), *cf.* equation (2). A similar explanation accounts for the formation of dimethylnitramine from t-butyldimethylamine in a mixture of nitric (90%) and concentrated sulphuric acid [equation (4)].[5]



$$Me_2NCMe_3 \xrightarrow[H_2SO_4]{HNO_3} Me_2\overset{+}{N}(NO_2)CMe_3 \longrightarrow Me_2NNO_2 + Me_3C^+ \quad (4)$$

Apparently the conversion of Dabco (**9**) into *N,N'*-dinitrosopiperazine (**22**) was blocked to a large extent by the formation

Table 1. Nitrosolysis of alkylpiperidines and dialkylpiperazines

Amine	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Nitrosamine	(15)	(15)	(15)	(15)	(22)	(22)	(22)	(22)
Yield (%)	80	72	Trace[a]	Trace[b]	90	81	55	8[d]
M.p. (b.p.)/°C	(95—97/ 12 mmHg[c])				155—157[e]			

[a] 60% of starting material recovered. [b] 42% of starting material recovered. [c] 218 °C/760 mmHg. C. Parr, *J. Org. Chem.*, 1959, **24**, 1325. [d] The mononitrate salt of (**23**) was the main product (45%), m.p. 178—180 °C (d) (Found: C, 40.75; H, 7.65; N, 23.75. Calc. for $C_8H_{18}N_4O_4$: C, 41.02; H, 7.75; N, 23.92%). [e] M.p. 156—156.5 °C, reported by M. V. George and G. J. Wright, in reference 15.

Table 2. Nitrosolysis of dimethylaminoalkanes

Amine	(10)	(11)	(12)	(13)	(14)
Dinitrosamine		(24)	(25)	(26)	(27)
Yield (%)[a]		68 (50)	48 (40)	41 (35)	58 (53)
M.p./°C		53—55[c]	64—66[d]	68—70[d]	58—60[d]
Dimethyl nitrosamine (%)[a,b]	90 (78)		43 (30)	38 (32)	35 (31)

[a] Yields determined by g.c. analysis of product mixtures; lower yields in parentheses represent isolation by chromatography on silica gel. [b] Identical with an authentic sample. [c] D. Seebach, R. Dach, D. Ender, B. Renger, M. Jansen, and G. Brachtel, *Helv. Chim. Acta*, 1978, **61**, 1622. [d] S. S. Brown, C. L. Leese, C. M. Timmis, and R. Wade, *J. Chem. Soc.*, 1963, 846.

Table 3. Nitrosolysis of functionalized methyldialkylamines

Amine	(17)	(18)	(19)	(20)	(21)
Nitrosamine	(24)	(31)	(32)	(22)	(30)
Yield (%)[a]	48	78	24	45	53
M.p./°C	53—55[b]	*c*	65—70[d]	155—157[e]	138—140[f]

[a] Isolated by column chromatography over silica gel. [b] Note *c*, Table 2. [c] Liq.: $\delta_H(CDCl_3)$ 2.6 (t), 2.9 (t), 3.1 (s), 3.8 (t), 3.9 (s), and 4.5 (t). [d] H. T. Nagasawa, P. S. Fraser, and D. L. Yuzo, *J. Med. Chem.*, 1973, **16**, 583. [e] Ref. 15. [f] (Found: C, 30.0; H, 5.05; N, 35.0. Calc. for $C_4H_8N_4O_3$: C, 30.00; H, 5.04; N, 34.99%).

of Dabco dinitrate which was insoluble in the medium and did not convert. It was separately shown that the dinitrate salt on heating gave compound (**22**) in low yield.

The diminished ability of dinitrogen tetraoxide in carbon tetrachloride to replace isopropyl and t-butyl groups at an amine nitrogen atom is in agreement with a previous report in which methylethylisopropylamine in acidified aqueous sodium nitrite gave low yields of methylisopropylnitrosamine (7—9%), ethylisopropylnitrosamine (7—10%), and a trace (1.3—1.5%) of methylethylnitrosamine; similar results were obtained with *N*,*N*-dimethylcyclohexylamine and *N*,*N*-dimethyl-2-(1,2,3,4-tetrahydro)naphthylamine, each of which gave dimethylnitrosamine in small amounts (2.1—5.9%) and the methylcycloalkylnitrosamine in yields of 59—73%.[6]

Since *N*,*N*′-dinitrosopiperazine (**22**) was obtained from *N*-nitroso-*N*′-methylpiperazine (**20**) in 45% yield it cannot be an intermediate in the conversion of *N*,*N*′-dimethylpiperazine (**5**) into the dinitrosodiamine (**22**) in 90% yield. In a similar reaction, *N*-nitro-*N*′-nitrosopiperazine (**30**) (53%) was obtained from *N*-nitro-*N*′-methylpiperazine (**21**) in a nitrosolysis reaction with dinitrogen tetraoxide. An explanation for this inhibition to nitrosolysis brought about by the presence of the nitrosamino or the nitramino group cannot be offered at this time.

An opposite effect was noted in the nitrolysis of certain *N*-t-butyl amines in which a nitro group attached at a β-carbon atom enhanced the formation of a nitramine by replacement of the t-butyl group. For comparison, the formation of dimethylnitramine from t-butyldimethylamine (devoid of nitro substituents) was much less efficient. Additional information will be sought to confirm and clarify this promotion in reactivity by a *C*-nitro group and a hindrance to reactivity by an *N*-nitroso or an *N*-nitro group.

A slight preference for the replacement of a methyl group rather than a methylene derivative was detected in a comparison of the formation of the dinitrosamine products (**25**)—(**27**) on the one hand and dimethylnitrosamine (**28**) on the other. It was of special interest to note that the latter was not produced in the reaction with 1,2-bis(dimethylamino)ethane (**11**) and was the only nitrosamine obtained from bis(dimethylamino)methane (**10**). The isolation of dimethylmethyleneammonium nitrate when the nitrolysis of the diamine (**10**) was interrupted before completion confirmed the proposed intermediacy of an aminium (radical cation) nitrate and its disproportionation to a methyleneammonium nitrate and a nitrate of the original amine. In a similar nitrosolysis, aqueous nitrous acid converted *N*-dimethylaminomethylpyrrole into dimethylnitrosamine.[6] Nitrosolysis of hexamethylenetetramine to R-Salt is, of course, a related reaction.

The failure of the nitrosolysis of 1,2-bis(dimethylamino)-ethane (**11**) to produce dimethylnitrosamine (**28**) was outstanding. Isolation of the intermediate diamine dinitrate when the nitrosolysis of the diamine (**11**) at 0 °C was interrupted after 30 min supported the previously proposed explanation for the conversion of a dimethylamino alkane into a methylnitrosaminoalkane. At the same time, it indicated that a 1,4-diradical dication was not present, insofar as the diradical would be expected to dissociate to the dimethyl methyleneammonium cation.

It was noted above that the formation of *N*,*N*′-dinitrosopiperazine (**22**) was considerably less efficient in the nitrosolysis of *N*-nitroso-*N*′-methylnitrosaminopiperazine than in the nitrosolysis of *N*,*N*′-dimethylpiperazine (**5**). A similar effect was noted in the efficiency of the formation of 1,2-bismethylnitrosaminoethane (**24**) which was lowered from 68% for conversion of the diamine (**10**) to 48% for conversion from 1-dimethylamino-2-methylnitrosaminoethane. The presence of the cyano group in β-dimethylaminopropionitrile had little, if any, adverse effect on the nitrosolysis to β-methylnitrosaminopropionitrile (78%). Nitrosolysis of α-dimethylaminoacetic acid gave α-methylnitrosaminoacetic acid.

Experimental

Instruments included Pye-Unicam SP200 (i.r.) Varian A-60 and T-60 (n.m.r.) Spectrometers. Elemental analyses were provided by Micro-Tech Laboratories, Inc., Skokie, Illinois. G.c. analyses were done in a HP-5790 instrument with a HP-3390-A integrator. (Column: 3% OV-17 on 80/100 Gas Chrom. Q Stainless Steel 6 ft. × 1/8 in.; carrier gas nitrogen; column temperature 100—200 °C with FID).

N-Methyl- and *N*-ethyl-piperidines (**1**) and (**2**), *N*-methyl-*N*′-methylpiperazine (**5**), 1,4-diazabicyclooctane (**9**), bis(dimethylamino)alkanes (**10**)—(**14**), β-dimethylaminopropionitrile (**18**), and α-dimethylaminoacetic acid (**19**) were commercially available.

N-Isopropyl- and *N*-t-butyl-piperidines (**3**)[7] and (**4**),[8] *N*-ethyl- and *N*-t-butyl *N*′-methyl-piperazines (**6**)[9] and (**8**),[10] 1-methylnitrosamino-2-dimethylaminoethane (**17**),[11] *N*-methyl-*N*′-nitrosopiperazine (**20**),[12] and *N*-methyl-*N*′nitropiperazine (**21**)[13] were prepared by literature procedures.

N-Isopropyl-*N*′-methylpiperazine (**7**)[14] was prepared from bis-(2-chloroethyl)-*N*-methylamine and isopropylamine (75%).

General Procedure.—Dinitrogen tetraoxide (excess) was added to a stirred solution of a tertiary amine (15 mmol) in carbon tetrachloride (15 ml), precooled to 0 °C. During the addition the temperature rose to 35—50 °C. The mixture was cooled to room temperature and stirring was continued overnight (14—16 h). Nitrogen oxides and solvent were removed under reduced pressure and the residue was partitioned between dichloromethane (50 ml) and saturated aqueous sodium chloride solution (50 ml). The aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give the products.

DABCO and Dinitrogen Tetraoxide.—Excess dinitrogen tetraoxide was added to 1,4-diazabicyclo-octane (**9**) (1.68 g, 15 mmol), suspended in carbon tetrachloride (15 ml), with cooling. During the addition, there was no rise in temperature. Stirring was continued overnight at room temperature. The reaction mixture was filtered to give a colourless solid (1.77 g, 70%). This was found to be the dinitrate salt of DABCO, m.p. 185—186 °C (decomp.).[1] The filtrate was concentrated to give (**22**) (0.33 g, 15%), m.p. and m.m.p. identical with authentic sample, 155—157 °C.[15]

t-Butylpiperidine (**4**) *and Nitronium Tetrafluoroborate.*—Nitroniumtetrafluoroborate, (1.32 g, 10 mmol) was added to a solution of compound (**4**) (1.41 g, 10 mmol) in absolute acetonitrile (20 ml) with stirring and cooling (ice-bath). After the addition, the reaction mixture was warmed slowly to 20 °C, stirred for 1 h and poured into water. The solution was extracted with dichloromethane (2 × 25 ml) and dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a liquid (0.49 g), t.l.c. and n.m.r. data of which showed it to be the starting amine (**4**) (35% recovery).

An experiment with nitrosonium tetrafluoroborate afforded similar results (32% recovery). In both cases there was no indication by t.l.c. comparison with authentic samples of the formation of either the *N*-nitro- or *N*-nitroso-piperidine.

t-Butylpiperidine (**4**) *with* 90% *Nitric Acid in Conc. Sulphuric Acid.*—The tertiary amine (**4**) (0.50 g, 3.6 mmol) was added to an excess of conc. sulphuric acid (18 ml) with cooling in ice.[5] To

this mixture was added at 0 °C a mixture of nitric acid (90%, 4.6 ml) and conc. sulphuric acid (7.5 ml). After the reaction had been stirred overnight at room temperature the solution was poured onto ice. Solid potassium carbonate was added to achieve pH 6. The mixture was extracted with dichloromethane, dried ($MgSO_4$), and concentrated. The residual liquid (0.19 g) was found to be the starting amine, (**4**) (38%), identified by t.l.c. and n.m.r. comparisons with authentic samples.

Acknowledgements

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