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18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Tert-Amines,
Nitrosamines,
Nitramines,
α-Substitution in Nitrosamines,
Nitrocyanocarbenes,
$S_{RN}1$ and related reactions,
Electron transfer,
Barrelene derivatives.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

A. For the efficient conversion of mono-tert-amines to nitrosamines treatment with dinitrogen tetroxide in an inert solvent at 0-45° has been developed. The replacement of dinitrogen tetroxide with other reagents led to lower yields and complicated product mixtures.

B. Attempts to oxidize the new R-salt carbinols A to RDX-ketones B have been unsuccessful. Apparently the heterocyclic ring was

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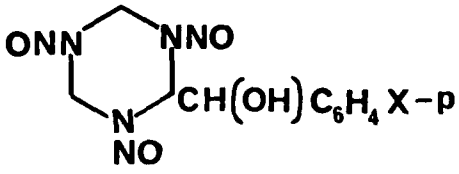
19 KEY WORDS (Continued)

20 ABSTRACT (Continued)

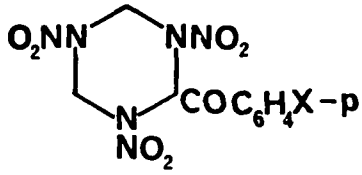
20. B. Continued

attacked and degraded.



A

X = H, NO_2

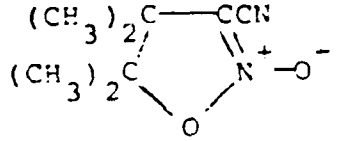


B

X = H, NO_2

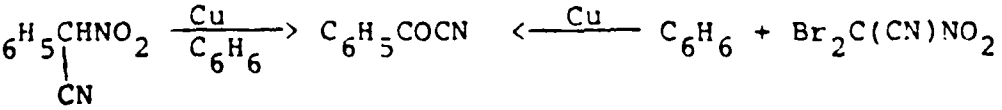
New attempts to achieve C-functionalization of RDX will be examined.

C. Uncatalyzed debromination of nitrodibromoacetonitrile by treatment with tetramethylethylene, dimethyl sulfide, and triethylamine under mild conditions gave respectively 3-cyano-4,4,5,5-tetramethylisoxazol-2-ine-2-oxide, dimethylsulfonium cyanonitromethylide, and triethylammonium cyanonitromethylide.

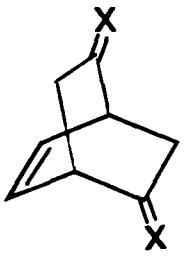


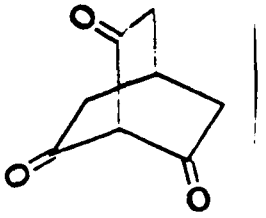
$(CH_3)_2\overset{+}{S}-\bar{C}(CN)NO_2$, $(C_2H_5)_3\overset{+}{N}-\bar{C}(CN)NO_2$

Base catalysed conversions ($S_{RN}1$ and related reactions) of nitroacetonitrile and phenylnitroacetonitrile were examined. Benzoyl cyanide was obtained from phenylnitroacetonitrile and from nitrodibromoacetonitrile in benzene.



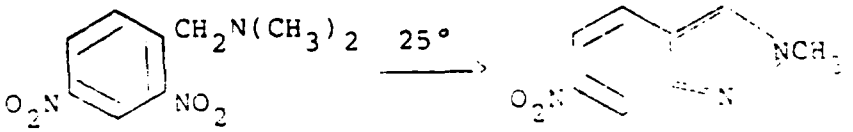
D. The known compounds 5,7-dioxo[2,2,2]bicyclooct-2-ene and 2,6,7-trioxo[2,2,2]bicyclooctane were prepared for investications designed to provide nitro derivatives. Oxime derivatives have been prepared for conversion to nitro derivatives.





X = O, NOH

E. Collaboration with Dr. M. D. Pace of the Naval Research Laboratory on the elucidation of electron transfer to give radical intermediates in the spontaneous conversion of N,N-dimethyl-2,4-dinitrobenzylamine to 6-nitro-2-methylindazole continued.



F. The writing of a book, "The C-Nitro Derivatives of N- and N,O-Five-membered Heterocycles" was completed. The book will be published by VCH Publishers, Inc. (was Verlag Chemie International, Inc.) in 1985.

Contents

A. Nitrosamines and Nitramines from Tertiary Amines.

With T. P. Pillai and V. T. Ramakrishnan

The following two reports were accepted for publication.

Nitrosamines from Tertiary Amines and Dinitrogen Tetroxide

(J. Chem. Soc.)

Abstract. A preparative nitrosolysis of aliphatic acyclic and cyclic tertiary monamines to nitrosamines was brought about by treatment with dinitrogen tetroxide in carbon tetrachloride at 0-45°. Dealkylation was restricted, where applicable, to demethylation. Competitive oxidation to an amide was observed in the formation of di-n-butylformamide from tri-n-butylamine. Diamine dinitrate salts, without nitrosamine formation, were obtained from 1,4-dimethylpiperazine and 1,4-diaza[2,2,2]bicyclooctane; however, each dinitrate salt thermolyzed at 180-200° to give a small amount of 1,4-dinitrosopiperazine. In acetic anhydride dinitrogen tetroxide converted amines less efficiently, gave lower yields of nitrosamines, was less selective in dealkylation, and introduced the formation of by-products.

Introduction. Both nitrolyses to give nitramines and nitrosolyses to give nitrosamines from aliphatic tertiary monamines have been erratic and often inefficient. To fulfill a need for the preparative conversion of trialkyl amines to nitramines[1] 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.[2]

Over 50 trialkyl and arylalkyl tertiary monamines showing a wide variety of structures have been investigated for nitrosolysis by nitrous acid. Under optimal conditions the amines $RR^1NCHR^2R^3$ and nitrous acid (4 to 10 molar ratio) in acetic acid (adjusted to pH 3.7 to 5) at 90° for 3 to 16 hours gave nitrosamines RR^1NNO (7% - 70%) and carbonyl compounds R^2R^3CO (up to 80%), often with low conversion of the amine.[3-6] A reaction between tri-n-butylamine and nitrous acid gave di-n-butylnitrosamine (6%), n-butyraldehyde (7%), di-n-butylamine (2%), an unsaturated tertiary amine, three aminoalcohols, and an aminoketone.[4]

Unstable complexes between a tertiary amine and dinitrogen tetroxide were formulated as $R_3\overset{+}{N}NO\ \overset{-}{O}NO_2$ and $R_3N \cdot nN_2O_4$ ($n > 1$).[7-10] Transnitrosation from triethylnitrosammonium nitrate was proposed to account for N-nitrosation of a secondary amine in the presence of triethyl amine and dinitrogen tetroxide in an inert solvent at -60° to 20°. Triethylamine was recovered.[11]

There is only one report of nitrosolytic dealkylation of tertiary amines by treatment with dinitrogen tetroxide. N,N-Dimethylaniline and its 4-nitro and 2,4-dinitro derivatives in carbon tetrachloride were converted to 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 benzyltrimethylammonium chloride were each unreactive.[12]

Explanations for nitrosolyes of tertiary amines by nitrous acid correlated structural effects and kinetic results in mechanism variations which held in common an iminium cation, $R_2\overset{+}{N}=CR_2$, as a key intermediate.[3-6] It was presumably formed by an elimination of nitroxyl from a nitrosammonium cation, produced from the amine and the nitrosonium cation, eq (1).[3]

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 to formamides, acetamides, and nitrosamines. It involved α-oxidation initiated by radical α-hydrogen abstraction by nitrogen dioxide generated in situ, eq (2).[13] 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[14] or by homolytic dissociation of a nitrosammonium cation, eq (3,4).[15] Since amine radical cations abstract hydrogen from CH bonds to form ammonium cations, eq (4),[14] presumptive evidence for the presence of a dimethylaniline radical cation, from the amine and dinitrogen tetroxide, is now found in the formation of the nitrated nitrosamine 4.

The conversion of an iminium cation intermediate to a nitrosamine and a carbonyl compound has been accounted for by two routes. In one hydrolysis to a secondary amine and a carbonyl compound was followed by nitrosation of the amine, eq (5).[3,6] In the other a dissociation of a hemiaminal nitrite ester occurred, eq (6).[4,5] In at least one example kinetic requirements disallowed the intermediacy of a secondary amine.[5a]

$$RCH_2NR_2 \xrightarrow{\overset{+}{N}O} RCH_2\overset{+}{N}(NO)R_2 \xrightarrow{-\ NOH} R_2\overset{+}{N}=CHR \qquad \text{eq (1)}$$

$$RCH_2NR_2 + 2NO_2(N_2O_4) \longrightarrow \underset{\bar{O}NO}{R_2\overset{+}{N}=CHR} + HNO_2 \qquad \text{eq (2)}$$

$$R_2NCH_2R \xrightarrow{N_2O_4} \underset{\bar{O}NO_2}{R_2\overset{+}{N}(NO)CH_2R} \longrightarrow \underset{\bar{O}NO_2}{\overset{+}{R_2N}CH_2R} + NO \qquad \text{eq (3)}$$

$$\underline{1} + \underset{\bar{O}NO_2}{R_2\overset{+}{N}=CHR} + \underset{\bar{O}NO_2}{R_2\overset{+}{N}HCH_2R} \rightleftharpoons \underset{O_2NO}{R_2NCHR} + R_2NCH_2R + HNO_3 \qquad \text{eq (4)}$$

$$R_2\overset{+}{N}=CHR \xrightarrow[-H^+]{\overset{H_2O}{-RCHO}} R_2NH \xrightarrow[-H^+]{\overset{+}{N}O} R_2NNO \qquad \text{eq (5)}$$

$$R_2\overset{+}{N}=CHR \xrightarrow[-H^+]{HONO} \underset{ONO}{R_2NCHR} \longrightarrow R_2NNO + RCHO \qquad \text{eq (6)}$$

Results and Discussion. Preparative conversions of tertiary aliphatic monamines 2-7 by treatment with dinitrogen tetroxide in carbon tetrachloride at 0°-45° gave nitrosamines 8-13, eq (7), (Table). A competitive oxidation to an amide was detected in the formation of di-n-butylformamide 14 (40%) from tri-n-butylamine 3. Attempts to extend the nitrosolysis to 1,4-dimethylpiperazine 15 and to 1,4-diaza[2,2,2]bicyclooctane 16 were unsuccessful; instead the diamine dinitrate salts (35%, 74%) were obtained. Thermolysis of each dinitrate salt at 180°-200° gave a small amount of 1,4-dinitrosopiperazine 17, eq (8).

Table

Nitrosamines from Tertiary Amines

A. With Dinitrogen Tetroxide in Carbon Tetrachloride

XYZN				XYNNO		
NO.	X	Y	Z	NO.	Yield, %[a]	bp, °C(torr)
2	C_2H_5	C_2H_5	C_2H_5	8	70 (51)	84-86 (50)[b]
3	n-C_4H_9	n-C_4H_9	n-C_4H_9	9	52 (42)	67-70 (0.4)[c,d]
4	$C_6H_5CH_2$	CH_3	CH_3	10	89 (84)	80 (0.3)[e]
5	$C_6H_5CH_2CH_2$	CH_3	CH_3	11	81 (70)	117-118 (2)[f]
6	$(CH_2)_4$		CH_3	12	42 (30)	103-105 (20)[g]
7	$(CH_2)_5$		CH_3	13	82 (58)	95-96 (12)[h]

B. With Dinitrogen Tetroxide in Acetic Anhydride[a]

Amine	2	3	4	5	6	7	19
Nitrosamine	8	9	10	11	12	13	10
Yield, %[a]	56[j]	42[j,k]	65[k,m]	62[j,k]	7[o]	34[j]	28[j,r]
Yield,[i] %[a]	16[j]	0[l]	87[k,n]	84[j,k]	0[p]	10[q]	0[k,s]

[a]Yields determined by gc analysis of product mixture; lower yields in parentheses represent isolation by distillation. Thermolysis during distillation left intractable tar residues. [b]174.5° (777 mm) reported: A. I. Vogel, J. Chem. Soc., 1948, 1833. [c]W. D. Emmons, K. S. McCallum, and J. P. Freeman, J. Org. Chem., 1954, 19, 1472. [d]Di-n-butylformamide 14 (40%) was also produced (see Experimental). [e]D. Seebach and D. Enders, Chem. Ber., 1975, 108, 1293. [f]D. Seebach and D. Enders, Angew. Chem. Internat. Ed. Engl., 1972, 11, 301. [g]P.A.S. Smith and H. G. Parr, J. Org. Chem., 1959, 24, 1325. [h]218° (760 mm) reported: C. Paal and W.-N. Yao, Chem. Ber., 1930, 63, 57. [i]Hydrochloric acid in the reaction mixture (see Experimental). [j]Amine conversion complete. [k]Small amounts of unidentified by products were also detected. [l]Amine recovered (88%). [m]Amine recovered (42%). [n]Amine recovered (19%). [o]Amine recovered (18%). [p]Amine recovered (19%). [q]Amine recovered (45%) [r]Benzaldehyde (58%) produced. [s]Amine recovered (60%; benzaldehyde obtained (13%).

Each amine 2-7 was completely consumed and gave a remarkably clean reaction. Analysis by gas chromatography of that portion of each product mixture insoluble in water revealed no additional products. By-products from alkyl group oxidation escaped as gases or were discarded with the water layer during workup. In one experiment with the amine 4 water was rigorously excluded from the reaction and was not added during workup. Gas chromatographic analysis of the residue which remained after the removal of volatile materials showed the presence of the nitrosamine 10 (91%) and did not detect the presence of another product. The fate of the methyl group lost in the reaction was not determined; presumably it was converted to formaldehyde and/or other oxidation products.

Favorable conditions permitted the expectation of an intermediate formation of iminium nitrate and nitrite salts (hemiaminal nitrate and nitrite esters), eq (1-4) and an equilibration between them maintained by the presence of dinitrogen tetroxide, eq (9). Nitrosamine formation was then accounted for by a thermolysis of the hemiaminal nitrite ester as was previously proposed, eq (6).[4,5] Thermolysis of a hemiaminal nitrate ester to a nitramine was not observed. A greater thermal stability of a nitrate ester was shown by the conversion of Eschenmoser's salt 18 to both the hemiaminal nitrate and nitrite esters by treatment with silver nitrate and nitrite, eq (10,11). Dissociation was observed only for the nitrite ester which gave dimethylnitrosamine. A similar observation of the greater thermal stability of a hemiaminal nitrate ester relative to a nitrite ester

was previously reported.[16]

$$\underset{\underline{2}\ -\ \underline{7}}{XYZN} + N_2O_4 \xrightarrow[0\text{-}45^\circ]{CCl_4} \underset{\underline{8}\ -\ \underline{13}}{XYNNO} + [ZONO_2] \qquad \text{eq (7)}$$

$(\underline{n}\text{-}C_4H_9)_2NCHO$ (14)

$XN(CH_2CH_2)_2NX$ — 15 X = CH_3; 17 X = NO

$N(CH_2CH_2)_3N$ (16)

$(C_6H_5CH_2)_2NCH_3$ (19)

$$\underline{19}\cdot(HNO_3)_2 \xrightarrow{180^\circ} \underline{17} \longleftarrow \underline{16}\cdot(HNO_3)_2 \qquad \text{eq (8)}$$

$$R_2\overset{+}{N}{=}CHR + N_2O_4(\overset{+}{N}O_2\bar{O}NO) \rightleftharpoons \underset{\bar{O}NO_2}{R_2\overset{+}{N}{=}CHR} + \underset{\bar{O}NO}{[N_2O_5]} \qquad \text{eq (9)}$$

$$\underset{\underline{18}}{(CH_3)_2\overset{+}{N}{=}CH_2\bar{I}} \xrightarrow[-AgI]{AgNO_3} [(CH_3)_2NCH_2ONO_2] \xrightarrow{25^\circ} (CH_3)_2NNO_2 \qquad \text{eq (10)}$$

$$\underline{18} \xrightarrow[-AgI]{AgNO_2} [(CH_3)_2NCH_2ONO] \xrightarrow{25^\circ} (CH_3)_2NNO \qquad \text{eq (11)}$$

Dinitrogen tetroxide in acetic anhydride also converted amines 2-7 to nitrosamines 8-13 but failed to convert dibenzylmethylamine 19 to benzylmethylnitrosamine 10 (Table). Small amounts of oxidation products (carbonyl derivatives) were detected by ir absorption but were not characterized further. Acetic anhydride was judged inferior to carbon tetrachloride as a solvent since the former failed to promote complete conversions of the amines and afforded lower yields of nitrosamines. Comparable results were obtained from the amines treated with

nitric acid in acetic anhydride.[13,18]

Addition of hydrochloric acid to the reaction mixture in acetic anhydride retarded amine conversion (except for amines 2 and 5) and lowered the yield of nitrosamine (except for nitrosamines 10 and 11) (Table). A reported[13] promotion of nitrosamine formation from 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.[17] 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.[18]

The addition of dinitrogen tetroxide to a tertiary amine, eg, 3 or 7, in dimethyl sulfoxide (DMSO) at -20° brought about a violent reaction with a 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 amines 4 and 5. Under the recommended optimal conditions[3] nitrous acid afforded the nitrosamines 10 (68%) and 11 (82%) with recovery of the amines 4 (41%) and 5 (50%). A complete conversion of 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 with the formation of nitrosamines in high yields. In further contrast with the results afforded by nitrous acid,[4] 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 di-n-butylformamide 14 (40%), was attributed to an α-oxidation.[13] 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 $15 \cdot 2HNO_3$ and $16 \cdot 2HNO_3$ 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, eq (4). In these examples α-hydrogen transfer to leave an iminium cation, eq (4), was not detected.

Certain observations need further clarification. There was unexpectedly an absence of aromatic ring nitration during the nitrosolysis of amines 4 and 5 with dinitrogen tetroxide in carbon tetrachloride to nitrosamines 10 and 11. In contrast a similar treatment of dimethylaniline gave N-methyl-N-nitroso-2,4-dinitro aniline (62%).[12,19,20]

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.[3-6]

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.[5b]

Experimental

Caution. Nitrosamines may be carcinogenic.

Instruments included Pye-Unicam SP-200 i.r., Varian A-60 and T-60 n.m.r. spectrometers. Elemental analyses were provided by Micro-Tech Laboratory, Skokie, Illinois. Product identifications and yields were determined by gc 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 x 1/8 in; carrier gas nitrogen; column temp. between 110° and 150°C, with FID).

The amines 2, 3, 4, 6, 7, 15, 16, and 19 and Eschenmoser's salt were commercially available. N,N-Dimethyl-β-phenethylamine 5 was prepared from β-phenethylamine and formaldehyde.[21] 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. Dimethyl nitramine and dimethylnitrosamine were obtained from dimethylcarbamoyl chloride and silver nitrate.[22]

General Procedure. Dinitrogen tetroxide (excess) was added to a

stirred solution of a tertiary amine (15mmol) in carbon tetrachloride (15 ml) precooled to 0°. During the addition the temperature rose to 40-50°. The mixture was cooled to 25°, stirred for 14 hours, treated with water (50 ml), and extracted with ether (3 x 100 ml) to give the mitrosamine (Table).

From the tri-n-butylamine 3 a mixture of di-n-butylformamide 14 and di-n-butylnitrosamine 9 was isolated after removal of ether and co-distilled at 62-64° (0.2 mm).[23] The distillate was shown by gc 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 excess of dinitrogen tetroxide in carbon tetrachloride (15 ml) at 0° gave an immediate precipitation of the diamine dinitrate, $15 \cdot (HNO_3)_2$. After separation by filtration the slightly hygroscopic salt was dried in a vacuum desiccator for 6 hours to give 1.23 g (35%), mp 212-214° (dec) after recrystallization from ethanol. Anal. calcd for $C_6H_{16}N_4O_6$: C, 30.00; H, 6.71; N, 23.32. Found: C, 29.55; H, 6.92; N, 23.50. 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°.

Similar treatment of 1,4-diaza[2,2,2]bicyclooctane 16 (a) with dinitrogen tetroxide in carbon tetrachloride gave the diamine dinitrate $16 \cdot (HNO_3)_2$ (74%), mp 185-186° (dec) after recrystallization from ethanol and (b) with nitric acid (100 %) in ether gave the dinitrate salt quantitatively. Anal. Calcd for $C_6H_{14}N_4O_6$: C, 30.25; H, 5.92; N, 23.52. Found: C, 30.13; H, 5.96; N, 23.46.

When the diamine 15 (150 mmol) and excess of dinitrogen tetroxide were mixed at 15 to 20° (no solvent) a violent reaction occurred with an evolution of flames and brown fumes and left an intractable tar in the flask.

Thermolysis of each salt 15·$(HNO_3)_2$ and 16·$(HNO_3)_2$ (150 mmol) in a small r.b. flask heated to 180-200° evolved copious amounts of brown fumes and left a tar residue. A chloroform extract from the residue gave an ir spectrum that was superposable throughout with an authentic spectrum obtained for 1,4-dinitrosopiperazine 17 prepared from piperazine and nitrous acid.[24]

To achieve rigorous exclusion of moisture in one experiment glassware was baked at 90° for 14 hours 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 it was dried by passing through Drierite. Water was not added during workup; instead the excess dinitrogen tetroxide and other nitrogen oxides (if present) were removed under vacuum. Gas chromatographic analysis of the residue showed the presence of the nitrosamine 10 (91%); no other material was detected.

Acetic anhydride as solvent. A mixture of dinitrogen tetroxide (excess) and N,N-dimethylbenzylamine 4 (15 mmol) in acetic anhydride (150 mmol), prepared at -5° and stirred at 25° for 14 h, gave the nitrosamine 10 (65%), a trace amount of amides

(ir 1635 and 1705 cm^{-1}), and recovered amine 4 (42%). Gc failed to detect benzaldehyde (10^{-7} mole would have been noted). Similar reactions with amines 2, 3, 5, 6, 7, and 19 were carried out (Table).

A mixture of dinitrogen tetroxide (excess), N,N-dimethylbenzylamine 4 (15 mmole), concentrated hydrochloric acid (5 mmole) and acetic anhydride (150 mmole), prepared at -5° and stirred at 25° for 14 h, gave the nitrosamine 10 (87%), trace amounts of amides (ir 1635, 1705, 1760 cm^{-1}), and recovered amine 4 (19%). Gc did not detect benzaldehyde. Similar reactions with amines 2, 3, 5, 6, 7, and 19 were carried out (Table).

Nitrous acid reactions. A solution 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 m) in water (50 ml) was adde
(45 minutes) and the mixture was stirred at 90° for two hours. It was cooled, diluted with water (50 ml) and extracted with ether (3 x 100 ml). The ether extract was washed with potassium carbonate solution (10%) until the aqueous layer was basic and with saturated salt solution, and dried ($MgSO_4$). Removal of the solvent left a yellow oil of benzylmethylnitrosamine 10 (1.20 g, 68%). The aqueous layer was made basic with potassium hydroxide and extracted with ether to recover dimethylbenzylamine (1.12 g, 41%).

A similar reaction with N,N-dimethyl-β-phenethylamine 5

gave the nitrosamine 11 (82% based on 50% recovery of the amine 5).

Nitrate and nitrite esters form Eschenmoser's salt.

Equimolar portions (5 mmol) of Eschenmoser's salt [$(CH_3)_2\overset{+}{N}=CH_2\ \bar{I}$], nmr ($CF_3CO_2H$): δ3.16 (s,6) and 6.46 (br s,2), and silver nitrite in acetonitrile (10 ml) was stirred at 25° for 16 hours. Precipitation of silver iodide was noted after 5 minutes and became quantitative. Dimethylnitrosamine was detected after 10 minutes and identified by tlc comparison with an authentic sample. In similar experiments Eschenmoser's salt failed to react with silver nitrate in acetonitrile at 25° for 5 days; however, in dry THF (10 ml) at 25° for 16 h a reaction gave a mixture of the hemiaminal nitrate ester [$(CH_3)_2\overset{+}{N}=CH_2\ \bar{N}O_3 \longleftrightarrow (CH_3)_2NCH_2ONO_2$], nmr ($CF_3CO_2H$): δ3.36 (s,6) and 7.50 (br s,2), and silver iodide (quantitative). Dimethylnitramine was not detected by either tlc or nmr; the authentic nitramine gave nmr (CF_3CO_2H): δ3.40 (s).

Nitrosamines and Nitramines from Tertiary Amines

(Synthesis)

In a newly developed preparative reaction tertiary aliphatic amines have been converted by nitric acid in acetic anhydride to nitrosamines. The method is a modification and extension of an isolated report on the oxidation of triethylamine 2 to diethylnitrosamine 8 (23%) and amides (15%) and of tri-n-butylamine 3 to N,N-di-n-butylformamide (major product) with small amounts of other amides and di-n-butylnitrosamine 9 by treatment with a mixture of nitric and acetic acids in acetic anhydride at 50°.[13,25]

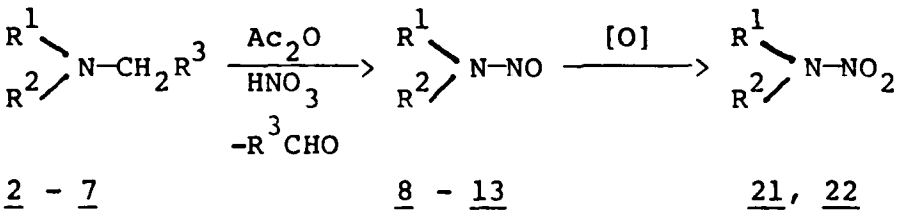
The new method offers a preparative alternative to unreliable nitrosolyses of tertiary amines by treatment with nitrous acid. For example tri-n-butylamine 3 and nitrous acid (50°, pH 3, 90 minutes) gave the nitrosamine 9 (6%), n-butyraldehyde (7%), di-n-butylamine (2%), an unsaturated tertiary amine, three aminoalcohols (trace), and an aminoketone.[4]

Since oxidation of a nitrosamine to a nitramine is available[2a,b] an overall conversion of a tertiary amine to a nitramine is also offered. A general need for the conversion of a tertiary amine to a nitramine has been cited.[1]

The amines examined included 2, 3, N,N-dimethylbenzylamine 4, N,N-dimethyl-β-phenethylamine 5, N-methylpyrrolidine 6, N-methylpiperidine 7, N,N'-dimethylpiperazine 15, 1,4-diazabicyclo-[2,2,2]octane 16, and N,N-dibenzylmethylamine 19.

A mixture of nitric acid in acetic anhydride (acetyl ni-

trate) and a tertiary amine, e.g., compound 4, was found to be stable at 25° for over ten hours. The mixture was activated by warming at 50° until the evolution of brown fumes of nitrogen dioxide became vigorous. Nitrosolysis, the major reaction, was detected for N-R bonds in amines 2 and 3 and for N-CH_3 bonds in amines 4 - 7 and accounted for the formation of nitrosamines 8-13 (Table) and aldehydes (undetected).[3,4] A competitive oxidation accounted for minor amounts of amides.[25]



2 - 7 8 - 13 21, 22

The diamine 15 gave the expected N,N-dinitrosopiperazine 17 (27%) but the structurally related bicyclic amine 16 gave an intractable mixture with no trace of the formation of the dinitrosamine 17.

$ZN(CH_2CH_2)_2NZ$

15 Z = CH_3

17 Z = NO

$N(CH_2CH_2)_3N$

16

$(C_6H_5CH_2)_2NCH_3$

19

Addition of hydrochloric acid to the reaction mixture introduced the Aqua Regia reaction and lowered the temperature required for the vigorous evolution of nitrogen dioxide. Contrary to an earlier claim[13,25] it did not improve the efficiency in

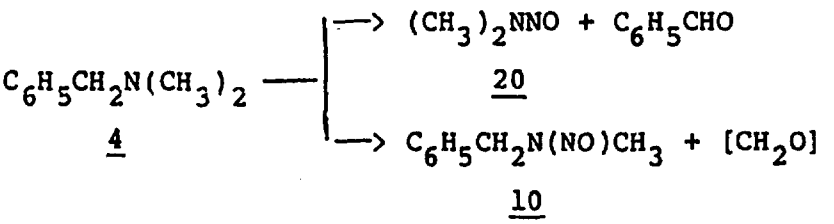
Table

Tertiary Amines $R^1R^2NCH_2R^3$ to Nitrosamines R^1R^2NNO

Amine	R^1	R^2	R^3	Nitrosamine	Yield % gc	Yield % distillation	bp, °C (mm) observed	bp, °C (mm) literature
2	C_2H_5	C_2H_5	CH_3	8	32	24	84-86 (50)	174.5 (777)[26]
3	n-C_4H_9	n-C_4H_9	n-C_3H_7	9	47	35	67-70 (0.4)	62-64 (0.2)[23]
4	CH_3	$C_6H_5CH_2$	H	10	76	58	80 (0.3)	80 (0.3)[27]
5	CH_3	$C_6H_5CH_2CH_2$	H	11	84	73	117-118 (2)	100 (0.1)[28]
6	$(CH_2)_4$		H	12	18	13	103-105 (20)	104-106 (20)[29]
7	$(CH_2)_5$		H	13	43	32	95-96 (12)	218 (760)[30]

the conversion of an amine to a nitrosamine with the possible exception of tri-n-butylamine 3 which gave the nitrosamine 9 in 47% yield in the absence of hydrochloric acid and 62% yield in the presence of hydrochloric acid; corresponding yields of 5% and 82% were previously reported.[13,25] A low conversion (14%) of N,N-dibenzylmethylamine 19 to benzaldehyde (33%) and the nitrosamine 10 (44%) was afforded by a similar reaction in the presence of hydrochloric acid. Nitric acid (100%) and anhydrous hydrogen chloride in acetic anhydride converted N,N-dimethylbenzylamine 4 to benzaldehyde (69%) and the nitrosamine 10 (26%). This result sharply contrasted with the conversion to the ni-

trosamine 10 (54%) with no detectable formation of benzaldehyde by treatment with nitric acid (70%) and hydrochloric acid (39%) in acetic anhydride. The formation of dimethylnitrosamine 20 in the former reaction was confirmed by tlc comparison with an authentic sample of the nitrosamine.



The nitrosamines 10 and 11 were oxidized by peracetic acid to N-methyl-N-nitrobenzylamine 21 ($R' = C_6H_5CH_2$, $R^2 = CH_3$) and N-methyl-N-nitro-β-phenethylamine 22 ($R' = C_6H_5CH_2CH_2$, $R^2 = CH_3$).

The amines 2, 3, 4, 6, 7, 15, 16, and 19 and the nitrosamines 8 and 9 were commercially available. N,N-Dimethyl-β-phenethylamine 5 was prepared from β-phenethylamine and formaldehyde.[21] Authentic samples of each nitrosamine 10,[31] 11[28] 12,[29] 13,[23] and 17 (mp 156-156.5° C)[24] were obtained from the appropriate secondary amine and nitrous acid.[21] Dimethylnitrosamine was obtained from dimethylcarbamoyl chloride and silver nitrate.[22] Caution is advised in working with nitrosamines which may be carcinogenic. Polynitrosamines may be explosive.

Amines and nitric acid in acetic anhydride. General Procedure.

Caution. Mixtures of nitric acid and acetic anhydride (acetyl nitrate) can be explosive at higher temperatures.[32]

Nitric acid (70%, 6.2 ml, 0.09 mol) was added dropwise with stirring to acetic anhydride (30 ml, 0.3 mol) maintained at 0°. An amine (0.03 mol) was added dropwise (about 10 minutes), the reaction mixture was warmed and kept at 50° for 30 minutes (evolution of dark brown fumes of nitrogen dioxide) and then stirred at room temperature for 16 hours. The mixture was poured onto crushed ice, treated with an excess of solid sodium hydroxide and thoroughly extracted with ether. After drying ($MgSO_4$) and concentration analysis by gas chromatography (gc) and distillation determined identification and yield of the nitrosamine (Table). The gc data was obtained from a HP-5790 instrument with a HP-3390A integration (column: 3% OV-17 on 80/100 Gas. Chrom Q, stainless steel 80 cm x 0.31 cm; carrier gas, nitrogen, column temp. between 110° and 150° C, with FID). Product identification and yield were determined by comparison with authentic data. Lower yields by distillation were attributed to thermolyses to intractable tars. The reaction with N,N-dimethylbenzylamine 4 also gave benzaldehyde (28%). The mixtures obtained from amines 2 - 7 also contained amides,[13,25] detected by ir.

Amines with nitric and hydrochloric acids in acetic anhydride. After a stream of anhydrous hydrogen chloride bubbled through a solution of N,N-dimethylbenzylamine 4 (4.05g, 30 mmol) and nitric acid (100%, 6.2 ml, 150 mmol) in acetic anhydride (30 ml, 30 mmol) at 0° for 15 minutes, the mixture was stirred at 25° for 16 hours. After the usual workup benzaldehyde (69%) and the

nitrosamine 10 (26%) were obtained.

In a related experiment nitric acid (70%, 6.2 ml, 90 mmol) and acetic anhydride (30 ml, 30 mmol) were mixed at 0°; the amine 4 (4.05g, 30 mmol) was added (10 minutes) and the mixture warmed to 50°. Hydrochloric acid (39%, about 0.5 ml) was added dropwise as a vigorous reaction with evolution of brown fumes of nitrogen dioxide occurred. The reaction mixture was cooled to 25° and hydrochloric acid (39%, 9.5 ml, 9.5 mmol) was added dropwise. After the reaction mixture was stirred at 25° for 16 hours 36% of the amine 4 was recovered and 54% was converted to the nitrosamine 10. Conversion to benzaldehyde was not detected (gc was sensitive to 10^{-7} mole). There was an unidentified product (<5%).

An experiment with methyldibenzylamine 19 and nitric acid in acetic anhydride with hydrochloric acid at 25° for 16 hours after mixing at 0° gave a low conversion (14%) to N-nitroso-N-methylbenzylamine 10 (44%) and benzaldehyde (33%). Neither dibenzylnitrosamine nor formaldehyde was detected.

Oxidation of nitrosamines to nitramines. N-Nitroso-N-methyl-β-phenethylamine 11 (0.55g, 3.3 mmol) dissolved in glacial acetic acid (10 ml), was treated with hydrogen peroxide (30%, 1 ml) dropwise, heated at 90° for 7 hours, cooled, diluted with crushed ice, and extracted with ether (3 x 50 ml). The ether extracts were washed with water, aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to give N-nitro-N-methyl-β-phenethylamine 22 (0.51g, 85%) as a yellow oil which crystallized from low boiling petroleum ether as a colorless solid mp 39-40°. Anal.

calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.95; H, 6.71; N, 15.55. (Elemental analyses were obtained from Mictro-Tech Laboratories, Skokie, Illinois). Ir($CHCl_3$): 1510(s) and 1290(s) cm^{-1} (NNO_2). Nmr ($CDCl_3$): δ2.95(t, 2H), 3.18 (s, 3H), 3.90(t, 2H) and 7.16(5H). (Spectroscopic data was obtained from Pye-Unicam 3-1200 ir and Varian A-60 nmr spectrometers).

When similarly treated N-methyl-N-nitrosobenzylamine 10 gave the nitramine 21 (87%) as a yellow oil, bp 95-97° (0.05 torr); lit bp 94-96° (0.05 torr);[33] ir ($CHCl_3$): 1510 (s) and 1285 (s) cm^{-1} (>NNO_2); nmr ($CDCl_3$): δ 3.37 (s, 3H), 5.02 (s, 2H), 7.37 (s, 5H).

Investigations on the diamines 15 and 16 and other unpublished results indicate important contrasts in reactivity with the monamines. The investigation should be extended to poly-tert-amines.

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B. C-Functionalization of R-Salt and RDX

with G. Kumar

A report published in Heterocycles and one published in J. Label. Cpd. and Radiopharm. follow.

Alkylation of Cyclic Gem-Dinitrosamines

(Heterocycles, 1984, 22, 2351)

Abstract - Alkylations with benzaldehyde catalyzed by potassium tert-butoxide converted 1,3,5-trinitrosohexahydro-1,3,5-triazine 1, 1,3-dinitrosoimidazolidine 3 and 1,3-dinitrosohexahydropyrimidine 4 to the 2-hydroxybenzyl derivatives (76 - 88%) and, in one instance, to the dialkylated product, 2,4-di-(hydroxybenzyl)-1,3,5-trinitrosohexahydro-1,3,5-triazine (40%). Lithium diisopropylamide was a less effective catalyst in alkylations with benzaldehyde or methyl iodide and was converted to diisopropylnitrosamine by transnitrosation. A catalytic amount of triethylbenzylammonium chloride promoted efficient mono-α-benzylations of nitrosamines 3 and 4 in aqueous sodium hydroxide at 25°C; however, simple nitrosamines failed to react and the trinitrosamine 1 was decomposed by the alkaline medium.

We wish to report the first examples of α-alkylation of polynitrosamines.[1] The project was undertaken in a search for ways to incorporate functional C-substituents in 1,3,5-trinitrosohexahydro-1,3,5-triazine 1 for oxidation to derivatives of 1,3,5-trinitrohexahydro-1,3,5-triazine 2 (RDX).

Both 1,3-dinitrosoimidazolidine 3 and 1,3-dinitroshexahy-

dropyrimidine 4 were readily converted to 2-alkyl derivatives. In tetrahydrofuran (THF) at -78°C potassium t-butoxide catalyzed alkylations with benzaldehyde to give the hydroxybenzyl derivatives 5 (88%) and 6 (76%). Attempts to alkylate further the dinitrosamines 5 and 6 in reactions with benzaldehyde and potassium t-butoxide at temperatures from -78° to -60°C were unsuccessful; the starting materials 5 and 6 were nearly quantitatively recovered. Lithium diisopropylamine (LDA) was less effective in a reaction (-80°C) with benzaldehyde to give the product 5 (42%). It also promoted a similar reaction with methyl iodide to give 2-methyl-1,3-dinitrosoimidazolidine 7 (60%). Instead of catalyzing methylation or benzylation of the dinitrosamine 4 LDA (-80°C) underwent transnitrosation to N-nitrosodiisopropylamine 8 (20%).[5] Efficient benzylations of the dinitrosamines 3 and 4 were brought about at 25°C in a phase transfer reaction with benzyl bromide in sodium hydroxide (50%) containing triethylbenzylammonium chloride. After 12 h 2-benzyl-1,3-dinitrosoimidazolidine 9 (79%) and 2-benzyl-1,3-dinitrosohexahydropyrimidine 10 (50%) were obtained. The latter yield was raised to 75% when two moles of benzyl bromide were initially present. Attempts to alkylate simple mononitrosamines in similar phase transfer reactions were unsuccessful.

Instead of promoting alkylations of the trinitrosamine 1, LDA underwent transnitrosation to the nitrosamine 8; the best yield of 8 (80%) was obtained from an excess of LDA (3.3 equivalents) at -80°C in the absence of an alkylating agent. The trinitrosamine 1 proved to be an efficient transnitrosating

agent toward amine anions; the highly hindered lithium 2,2,6,6-tetramethylpiperidide[6] was converted (40%) to the nitrosamine 11.[7]

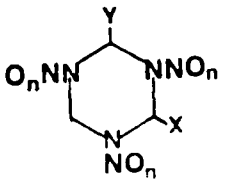
Sodium hydroxide solutions slowly dissolved the trinitrosamine 1 with an evolution of an ammoniacal odor indicating ring degradation. At room temperature the trinitrosamine was unaffected by either sodium or potassium hydride but decomposition on heating with sodium hydride was slow, faster with potassium hydride.

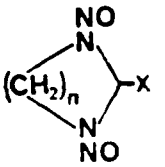
Alkoxides catalyzed mono- and dialkylation of the trinitrosamine 1 with benzaldehyde to give 2-hydroxybenzyl- 12 and 2,4-dihydroxybenzyl-1,3,5-trinitrosohexahydro-1,3,5-triazine 13. Potassium t-butoxide at -80°C afforded the monoalkylation product 12 (79%) and in a separate operation catalyzed the conversion of the latter to the dialkylated product 13 (40%). The assignment as a 2,4-disubstituted derivative 13 rather than a 2,2-disubstituted isomer is tentative. It was supported by examples in which axial but not equatorial hydrogen at an adjacent carbon atom was replaced by an alkyl group in similar reactions with cyclic mononitrosamines.[8] Also the replacement of only one hydrogen (presumably axial) at C-2 in the dinitrosamines 3 and 4 was noted. An unresolved complexity of ^{1}H and ^{13}C nmr spectra was partially attributed to the presence of geometrical nitrosamine isomers.[9]

Attempts to further alkylate compound 13 with benzaldehyde at low temperatures under the catalysis of potassium t-butoxide led to the recovery of compound 13 (75%). At higher temp-

eratures complex mixtures were obtained as shown by tlc. Reversibility[10] of the alkylation with benzaldehyde was demonstrated by treatment of product 12 in t-butyl alcohol with a catalytic amount of potassium t-butoxide at 25°C to give benzaldehyde, identified by nmr and the dinitrophenylhydrazone derivative, and the trinitrosamine 1.

Attempts to achieve other base catalyzed reactions between the trinitrosamine 1 and methyl iodide, ethyl iodide, benzyl bromide, formaldehyde, n-propyl nitrite, p-toluenesulfonylazide, and O-methylhydroxylamine were unsuccessful.





1 n = 1, X = Y = H

2 n = 2, X = Y = H

12 n = 1, X = $CH(OH)C_6H_5$, Y = H

13 n = 1, X = Y = $CH(OH)C_6H_5$

3 n = 2, X = H

4 n = 3, X = H

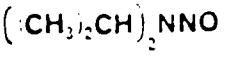
5 n = 2, X = $CH(OH)C_6H_5$

6 n = 3, X = $CH(OH)C_6H_5$

7 n = 2, X = CH_3

9 n = 2, X = $CH_2C_6H_5$

10 n = 3, X = $CH_2C_2H_5$



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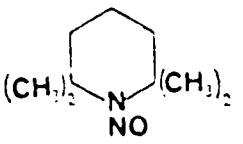


11

EXPERIMENTAL

Preparations of 1,3,5-trinitroso-1,3,5-triazine 1,[9] and 1,3-dinitrosohexahydropyrimidine 4[11] followed literature procedures. Instruments included spectrometers: Pye-Unicam ir SP200, and Hewlett-Packard GCMS 5985. Elemental analyses were provided by Micro-Tech Laboratories, Skokie, Illinois.

1,3-Dinitrosoimidazolidine 3. To a mixture of ethylenediamine (30.0 g, 0.50 mol) and aqueous formaldehyde (37.5 g, 0.50 mol) prepared and stored at 0°C for 2 h a solution of sodium nitrite (69.0 g, 1.0 mol) in water (200 ml) and sulfuric acid (26%, 235 ml) were added simultaneously as the temperature was kept below 5°C. After the mixture was stirred at 5°C for 1 h the product 3 was separated as a light yellow solid (20.0 g, 31%) mp 38-40°C after purification by recrystallization from a mixture of ether and petroleum ether; ir (KBr): 1440 cm^{-1} (NO). Anal. calcd. for $C_3H_6N_4O_2$: C, 27.70; H, 4.65; N, 43.06; found: C, 27.56; H, 4.71; N, 43.11.

2-Hydroxybenzyl-1,3-dinitrosoimidazolidine 5 .- To LDA (0.59 g, 5.5 mmol) in THF (40 ml) at -90°C 1,3-dinitrosoimidazolidine 3 (0.65 g, 5.0 mmol) in THF (5 ml) followed by benzaldehyde (0.53 g, 5.0 mmol) were added and the mixture was stirred for 3 h. Acetic acid (0.33 g, 5.5 mmol) was added and the solution was allowed to warm to 25°C. THF was removed by evaporation and the residue dissolved in methylene chloride (50 ml) was washed with a saturated solution of sodium chloride, dried, and evaporated to give the product 5 as a yellow gum which became a yellow

solid (0.50 g, 42%), mp 87-90°C after recrystallization from a mixture of ether and petroleum ether. Ir (KBr): 3380 (OH), 1440 cm^{-1} (NO); m/e (70 eV): 237 $(M+1)^+$ (2%), 206 $(M-30)^+$ (1%), 79 $(C_6H_7)^+$ (100%) Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.76; H, 5.10; N, 23.74.

2-Methyl-1,3-dinitrosoimidazolidine 7. A similar procedure gave the product 7 as a yellow oil (60% yield) purified by pot to pot short path distillation (bath temperature 110-130°C, 0.1 Hg mm). Ir (thin film): 1440 cm^{-1} (NO); m/e (70 eV): 144 M^+ (2%), 114 (7%), 70 (100%). Anal. calcd for $C_4H_8N_4O_2$; C, 33.33; H, 5.59; N, 38.81. Found: C, 33.69; H, 5.54; N, 38.37.

2-Hydroxybenzyl-1,3-dinitrosoimidazolidine 5. A mixture of 1,3-dinitrosoimidazolidine (0.65 g, 5.0 mmol) and benzaldehyde (0.53 g, 5.0 mmol) in THF (5 ml) was added to potassium t-butoxide (0.56 g, 5.0 mmol) in THF (50 ml) at -78°C and the mixture was held at this temperature for 2 h. After workup as described above the product 5 was obtained as a light yellow solid (1.04 g, 88%), mp 86-90°C. A tlc analysis and ir analysis showed the product to be identical with the sample previously obtained.

2-Hydroxybenzyl-1,3-dinitrosohexahydropyrimidine 6. A similar procedure gave the product as a yellow gum (76%). Treatment with acetic anhydride gave the acetate ester derivative as a yellow solid, mp 110-114°C after recrystallization from ether. Ir (KBr): 1750 (CO), 1450 cm^{-1} (NO). Anal. calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.36; H, 5.58; N, 19.21.

2-Benzyl-1,3-dinitrosoimidazolidine 9. A mixture of 1,3-

dinitrosoimidazolidine 3 (0.65 g, 5.0 mmol), benzyl bromide (0.86 g, 5.0 mmol), and a catalytic amount of benzyltriethylammonium chloride in sodium hydroxide (50%, 5 ml) was stirred for 16 h, diluted with water (25 ml), and extracted with ether (2 x 25 ml). The organic layer was washed with water, dried, and evaporated to leave the product 9 as a yellow viscous oil (0.87 g, 79%) which solidified on standing and gave a mp 70-72°C after recrystallization from a mixture of ether and petroleum ether. Ir (KBr): 1450 cm^{-1} (NO); m/e (70 eV): 220 M^+ (0.07%), 91 (100%). Anal. calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.64; H, 5.56; N, 25.33.

2-Benzyl-1,3-dinitrosohexahydropyrimidine 10. - A similar procedure with two equivalents of benzyl bromide gave the product 10 (75%) as a yellow viscous oil. Ir (thin film): 1450 cm^{-1} (NO); m/e (70 eV): 235 $(M+1)^+$ (0.1%), 91 (100%) Anal. calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.49; H, 6.07; N, 23.69.

2-Hydroxybenzyl-1,3,5-trinitrosohexahydro-1,3,5-triazine 12 . - A mixture of 1,3-5-trinitrosohexahydro-1,3,5-triazine 1 (0.87 g, 5.0 mmol) and benzaldehyde (0.53 g, 5.0 mmol) was added to potassium t-butoxide (0.56 g, 5.0 mmol) in THF (50 ml) at -78°C and stirred at this temperature for two hours. Acetic acid (0.30 g, 5.0 mmol) was added and the mixture was warmed to 25°C. THF was removed by evaporation and the residue dissolved in methylene chloride (50 ml) was washed with a saturated solution of sodium chloride, dried, and evaporated to give the product 12 as a light yellow solid (1.10g, 79%), mp 123-126°C

after recrystallization from a mixture of ether and petroleum ether. Ir(KBr): 3450 (OH) and 1500 cm^{-1} (NO); m/e (70 eV): 281 $(M+1)^+$ (0.13%), 107 (100%). Anal calcd. for $C_{10}H_{12}N_6O_4$: C, 42.86; H, 4.28; N, 30.00. Found: C, 43.00; H, 4.27; N, 30.31.

2,4-Di(hydroxybenzyl)-1,3,5-trinitrosohexahydro-1,3,5-triazine 13 . - In a similar reaction the monoalkylated trinitrosamine 12 was stirred at -78°C for three hours and stored at -60°C for 2 h before proceeding as described above to give a mixture after washing with a saturated solution of sodium chloride, drying, and removing methylene chloride by evaporation. The crude mixture was applied to a silica gel column. Methylene chloride eluted unreacted benzaldehyde (40%) and the trinitrosamine 12 (29%). Further elution gave the product 13 (40%) as a light yellow gum which became a powder, mp 166-169°C after trituration with a mixture of ether and petroleum ether. Recrystallization from a mixture of ether and petroleum ether gave a yellow solid, mp 170-174°C. Ir(KBr): 3450 (OH) and 1500 cm^{-1} (NO); m/e (70 eV): 107 (100%). Anal. calcd for $C_{17}H_{18}N_6O_5$: C, 52.85; H, 4.70; N, 21.75. Found: C, 53.23; H, 5.10; N, 21.89.

1,3,5-Trinitroso- and 1,3,5-Trinitrohexahydro-1,3,5-Triazine-$^2H_6$ (J. Labelled Compounds and Radiopharmaceuticals, accepted).

Summary. Perdeuteration of 1,3,5-trinitrosohexahydro-1,3,5-triazine was brought about by treatment with potassium alkoxide in CH_3O^2H(99.5%). The important high energy compound, 1,3,5-trinitrohexahydro-1,3,5- triazine (RDX), was obtained in its perdeuterated modification (>99% ^2H) by oxidation of the perdeuterated trinitrosamine with a mixture of nitric acid (100%) and hydrogen peroxide (30%).

We wish to report a preparation of 1,3,5-trinitrosohexahydro-1,3,5-triazine-$^2H_6$ 14 by deuterium exchange and its subsequent oxidation to 1,3,5-trinitrohexahydro-1,3,5-triazine-$^2H_6$ (RDX-$^2H_6$, 15) (>99% ^2H). This preparation of the nitramine 15 offers several advantages over an alternative preparation from $O{=}C^2H_2$, N^2H_3, $N^2H_4NO_3$, $CH_3CO_2{}^2H$, and $^2HNO_3$.[12] It removes the possibility of contamination by 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane-$^2H_8$ (HMX-$^2H_8$) an expected by-product since HMX formation can accompany RDX formation in the nitrolysis of hexamethylenetetramine.[13] Also it is more economical in the consumption of deuterium; its efficiency is greater (74% vs 58%), and it is a convenient operation.

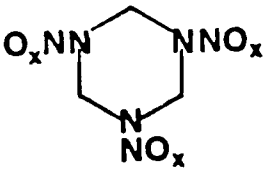
The base catalyzed α-deuteration of simple nitrosamines was first reported in 1970[13] and reviews of the reaction have appeared.[3,4] Monofunctional nitrosamines generally resist alkaline degradation, have been distilled from 3N sodium hydroxide[14] and have undergone α-deuteration in $NaO^2H/^2H_2O$ at

100°.[2-4]

Attempts to deuterate 1,3,5-trinitrosohexahydro-1,3,5-triazine 16 in the presence of either aqueous alkali or lithium diisopropylamide were unsuccessful and resulted, instead, in ring degradation. As the nitrosamine was consumed on treatment with sodium hydroxide (40%) at 25° an ammoniacal odor was noted (a similar degradation of 1-nitroso-3,5-dinitrohexahydro-1,3,5-triazine when heated in sodium hydroxide (10%) was reported).[13] Extensive transnitrosation to the lithium amide gave diisopropylnitrosamine (18), isolated in good yield. Similar reactions were known to be competitive with α-deuteration when certain simple nitrosamines were treated with lithium amides.[3]

Potassium tert-butoxide or methoxide catalyzed deuterium exchange at 25° between CH_3O^2H (99.5% ^2H) and 1,3,5-trinitrosohexahydro-1,3,5-triazine (16) to give quantitatively the perdeutero modification 1. Progress of the reaction was monitored by the disappearance, complete in 15 minutes, of ^1H nmr signals at δ 5.66, 6.28, and 6.92 characteristic of the nitrosamine 16.[15] Recyclization insured the quantitative formation of analytically pure product 14, $C_3{}^2H_6N_6O_3$.

Oxidation of the trinitrosamine 14 by a mixture of nitric acid (100%) in hydrogen peroxide (30%) gave RDX-$^2H_6$ 15 (70%). A similar oxidation 16 → 17(74%) was reported.[2] The FD mass spectrum showed the molecular ion M^+ at 228 (100%) and contained no evidence for the presence of contamination with partial deuteration products with masses 222-227.



14, X = 1, H = ^2H

15, X = 2, H = ^2H (RDX-$^2H_6$)

16, X = 1, H = ^1H

17 X = 2, H = ^1H (RDX)

$((CH_3)_2CH)_2NNO$

18

EXPERIMENTAL

Melting points were determined from a Thomas-Hoover mp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM 360A spectrometer using TMS as an internal standard. Mass spectra were obtained from a Field Ionization and from a Field Desorption mass spectrometer (see Acknowledgment).

The 1,3,5-trinitrosohexahydro-1,3,5-triazine (16) was prepared from the condensation of formaldehyde and ammonia followed by the nitrosolysis of hexamethylenetetramine.[13a] Methanol-O-^2H (99.5% ^2H) was obtained from Aldrich Chemical Company.

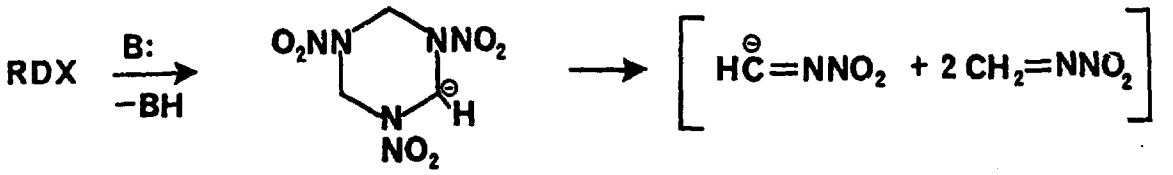
1,3,5-Trinitrosohexahydrohexahydro-1,3,5-triazine-$^2H_6$ (14). A solution of the nitrosamine 16 (0.174 g, 1.0 mmol) and potassium methoxide (1.0 ml of a 0.001 M solution of potassium methoxide in CH_3O^2H) in CH_3O^2H (5.0 ml) at 25° completed deuterium exchange within 15 minutes as shown by ^1H nmr monitoring. After the solvent was removed by evaporation, the residue, dissolved in methylene chloride, was washed with ^2H_2O and dried. Removal of methylene chloride by evaporation left perdeuterated 1,3,5-trinitrosohexahydro-1,3,5-triazine (14) as a colorless

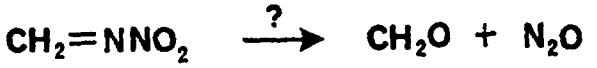
solid, 0.16 g (90%) mp 102-103° after recrystallization from ethanol. Anal. Calcd for $C_3{}^2H_6N_6O_3$: C, 20.00; ^2H, 6.71; N, 46.65. Found: C, 20.03; ^2H, 6.50; N, 46.29. Ir(KBr): 2280 (C-^2H) and 1475 cm^{-1} (N=O). FIMS m/e: 180 M^+ (100%), 179 (15%) To insure complete deuteration the product was recycled under the same conditions.

1,3,5 -Trinitrohexahydro-1,3,5-triazine-$^2H_6$ (15). To a mixture of hydrogen peroxide (30%, 0.71 g, 6.3 mmol) and nitric acid (100%, 9.2 g, 142 mmole) the deuterated nitrosamine 14 (0.31 g, 1.7 mmol) was added slowly at -40°. The reaction mixture was warmed and held at 20° for 5 minutes, and poured onto crushed ice (20 g) to precipitate 1,3,5-trinitrohexahydro-1,3,5-triazine-$^2H_6$ 15 as a colorless solid (0.27 g, 71%), mp 201-202° after recrystallization from acetic acid. Anal. Calcd for $C_3{}^2H_6N_6O_6$: C, 15.79; ^2H, 5.30; N, 36.83. Found: C, 15.76; ^2H, 5.25; N, 36.55. Ir (KBr): 2300 (C-^2H), 1525 and 1340 cm^{-1} (NO_2). FDMS m/e 228 M^+ (100%).

Molar excesses of either potassium methoxide or sodium hydroxide completely degraded RDX 2; the formaldehyde produced was detected by its characteristic odor. It was assumed that the reaction was initiated by abstraction of a proton and that this left a carbanion which underwent ring degradation faster than it could be captured in an alkylation reaction, eq (1). In partial contrast the anion from R-salt 1 was alkylated by aldehydes and ketones but it also underwent ring degradation on

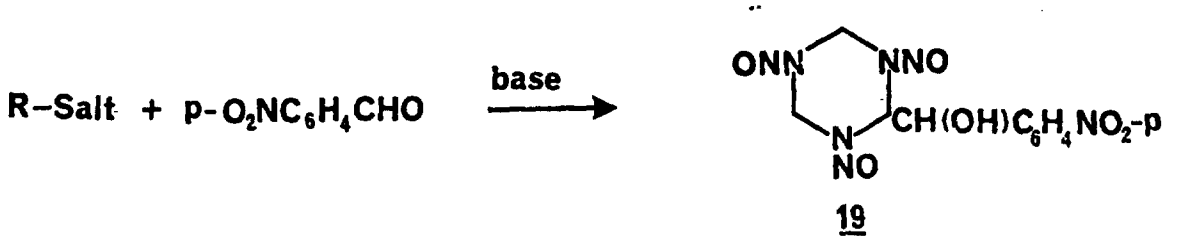
attack by base.





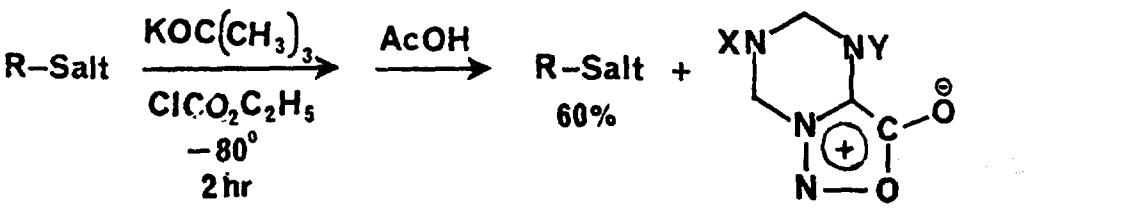
eq (1)

R-Salt has been alkylated with benzaldehyde (above), p-nitrobenzaldehyde, and acetone. Attempted alkylation with formaldehyde failed probably due to the existence of formaldehyde as its trimer at -80°, the optimum temperature for alkylations. Stoichiometry expected to lead to dialkylation by p-nitrobenzaldehyde afforded instead only a slightly better yield of the monoalkylation product 19 eq (2).



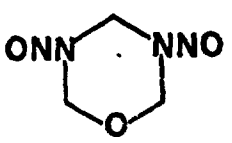
eq (2)

Acylation of R-salt by ethyl chloroformate went beyond the formation of the expected product to give a product 20, $C_7H_9N_5O_5$. The proposed structure as shown fulfilled analytic and spectroscopic requirements; nevertheless this assigned structure has not been confirmed. Replacement of a nitroso group at nitrogen with a carboethoxy group is unusual, eq (3).



20 (25%) X=$CO_2C_2H_5$, Y=NO
or X=NO, Y=$CO_2C_2H_5$

eq (3)



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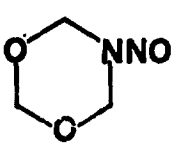

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Nitrosamine sensitivity to protic acids was an expected property of R-salt. Lewis acids also were found to be reactive. Both nitrosonium and nitronium tetrafluoroborate converted R-salt to the oxide 21[16] and probably the dioxide 22. Dinitrogen tetroxide converted R-Salt to gaseous products with the odor of formaldehyde. RDX was unaffected by similar treatment with these three reagents.

Considerable attention was given to the oxidation of alcohols 12 and 19 to the corresponding ketones. Intractable product mixtures were obtained in reactions with (a) oxalyl chloride in dimethyl sulfoxide, (b) pyridinium chlorochromate, (c) t-butylammonium permanganate, (d) dichlorodicyanoquinone, (e) nitrosonium tetrafluoroborate, (f) dinitrogen tetroxide, and (g) activated manganese dioxide.

The alcohol 12 in an excess of nitric acid (100%) gave a light yellow solid, $C_{10}H_{10}N_8O_{12}$, 23 (40%). Similar treatment converted the alcohol 19 to a light yellow solid, $C_9H_9N_5O_8$, 24. It is believed that both reactions brought about changes to the heterocyclic ring. Suggested structures shown are in agreement with analytical and spectroscopic evidence however they have not been more firmly established.

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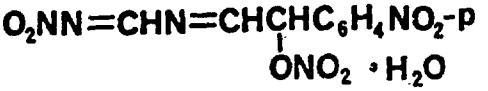
$C_{10}H_{10}N_8O_{12}$



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$C_9H_7N_5O_7 \cdot H_2O$

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C. Chemistry of Nitrocyanocarbene

With T. Manimarin and V. T. Ramakrishnan

Dibromonitroacetonitrile 1 came to our attention in a search for the preparation of unknown dicyanodinitroethylene 2.[1] An examination of the facile loss of bromine from the dibromide 1 brought about the following report accepted for publication in Chemical Communications.

$Br_2C(NO_2)_2CN$ $O_2NC(CN)=C(CN)NO_2$

1 2

Nitrocyanocarbene Derivatives from Nitrodibromoacetonitrile

Summary. Uncatalyzed debromination of nitrodibromoacetonitrile 1 by treatment with tetramethylethylene, dimethyl sulfide, and triethylamine under mild conditions gave respectively 3-cyano-4,4,5,5-tetramethylisoxazol-2-ine-2-oxide 4, dimethylsulfonium cyanonitromethylide 5, and triethylammonium cyanonitromethylide 6.

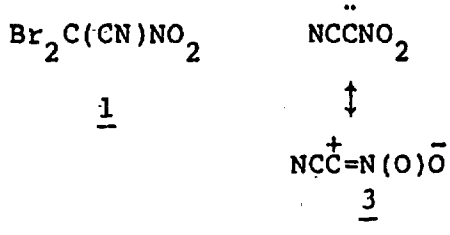
Although reactions of nitrocarbenes were considered unknown as recently as 1973,[2] isoxazolines and isoxazoline-N-oxides thought to be derived from such an intermediate have been obtained from the hazardous thermolysis of metal salts of gem-dinitroalkanes[3-5] and from silyl derivatives of trinitromethane;[6] but other attempts to generate a nitrocarbene failed.[7] We now report simple and efficient uncatalyzed conversions of nitrodibromoacetonitrile 1[8] to 3-cyano-4,4,5,5-tetramethylisoxazol-2-ine-2-oxide 4,[9] dimethylsulfonium and triethylammonium cyanonitromethylides 5 and 6[9] presumably via the intermediacy of nitrocyanocarbene 3.

The methylide 5 was previously obtained from nitroacetonitrile and dimethyl sulfoxide.[10]

In methylene chloride at 25°C for 30 minutes two equivalents of tetramethylethylene debrominated the dibromo compound 1 to give 2,3-dibromo-2,3-dimethylbutane 7, 42%, mp 168-169°C (dec)[11] and the heterocycle 4, 45%, mp 68-69°C (with sublimation). The structure 4 was confirmed by an x-ray determination[12]

The dibromo compound 1 was also debrominated by similar treatment with dimethyl sulfide and with triethylamine to give the cyanonitromethylides 5, 80%, mp 213-214°C (dec)[10] and 6, 5%, mp 154-155°C (dec). Triethylammonium bromide, 45%, mp 247-249°C (dec)[13] was also obtained.

Further work on the dehalogenation of negatively substituted nitrodibromomethanes is underway.



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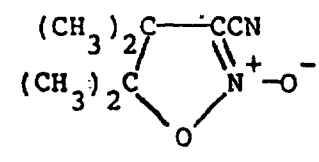

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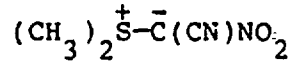

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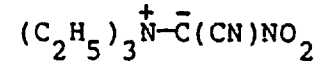

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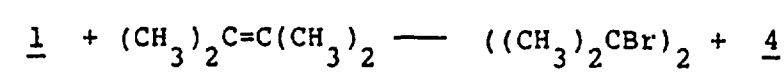

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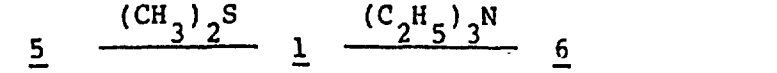


The dibromide 1 readily reacted with the dianion 8 of nitroacetonitrile but the expected olefin 2 was not detected in the intractable product mixture. Methyl iodide and benzyl bromide each converted the dianion to similar product mixtures; however the latter also offered low yields of the expected dibenzyl derivative 9 and 1,1,2-tribenzyl-1,2-dicyano-2-nitroethane 10. A nitrocarbanion displacement of a nitrite anion can account for the formation of product 10, eq (1). Similar reactions have been described by N. Kornblum, eq (2).[14] They have been designated $S_{RN}1$.

$[NCCNO_2]^=$ (8) $(C_6H_5CH_2)_2C(CN)NO_2$ (9) $(C_6H_5CH_2)_2C(CN)-C(CN)CH_2C_6H_5$ (10), with NO_2 on the second carbon

$$C_6H_5CH_2\overset{\overset{CN}{|}}{\bar{C}}NO_2 + \underline{9} \longrightarrow \underline{10} + NO_2^- \qquad \text{eq (1)}$$

$$R_2\bar{C}NO_2 + R_2C(CN)NO_2 \longrightarrow R_2C(CN)NO_2^{\cdot -} + R_2\dot{C}NO_2$$

$$R_2C(CN)NO_2^{\cdot -} \longrightarrow R_2\dot{C}CN + NO_2^-$$

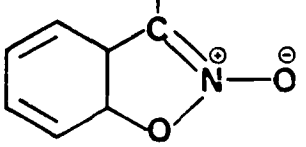
$$R_2\dot{C}CN + R_2\bar{C}NO_2 \longrightarrow R_2C(CN)CR_2NO_2^{\cdot -}$$

$$R_2C(CN)CR_2NO_2^{\cdot -} + R_2C(CN)NO_2 \longrightarrow R_2C(CN)CR_2NO_2 + R_2C(CN)NO_2^{\cdot -} \qquad \text{eq (2)}$$

The presence of freshly precipitated copper promoted the formation of benzoyl cyanide 11 (28%) when the dibromide 1 was heated in benzene for 15 hours. α-Nitrobenzyl cyanide 12, a

proposed intermediate, was independently shown to give benzoyl cyanide (97%) in the presence of copper. Insofar as dicyanocarbene combined with benzene by addition rather than by insertion[15] it was proposed that the initial reaction between the carbene 3 and benzene gave an isoxazoline intermediate, eq (3). That conversion of compound 12 to product 11 did not proceed from a nitronate was shown by observing no reaction when the sodium salt 13 was heated in benzene in the presence of copper. The conversion can be explained by an isomerization of the nitro compound 12 to a nitrite ester 14 followed by an elimination of nitroxyl, eq (4). A radical process for such an isomerization of an α-nitronitrile has been proposed.[16] Thermolysis of α-bromo-α-nitrobenzyl cyanide 15 to product 11, eq (5)[17] tends to support the nonparticipation of a nitronic acid tautomer and to support an isomerization to a nitrite ester in the conversion 12 → 11.

C_6H_5COCN (11) $\quad C_6H_5CH(CN)NO_2$ (12) $\quad C_6H_5C(CN)=NO_2Na$ (13) $\quad C_6H_5CH(CN)ONO$ (14)

$Br_2C(CN)NO_2 \xrightarrow[-CuBr_2]{C_6H_5,\ Cu}$  $\longrightarrow$ 12

12 → 11 + [NOH] eq (3)

12 → $C_6H_5\dot{C}HCN + NO_2$ → 11 → 11 + [NOH] eq (4)

$C_6H_5\overset{Br}{\underset{CN}{C}}NO_2$ (15) → 11 + [NOBr] eq (5)

An unexpected formation of the oxime 16 (29%) of p-nitrobenzoyl cyanide occurred when the cyanide 12 was heated alone in benzene, eq (6). Apparently the C-nitro compound 12 served as both a nitrosating and a nitrating agent. A low yield (2%) of the oxime 16 was previously obtained when the cyanide 12 was treated with sodium nitrite in acetone.[18]

$$\underline{12} \xrightarrow{80^{\circ}} \underset{\underline{16}}{p\text{-}O_2NC_6H_4C(=NOH)CN} \qquad \text{eq (6)}$$

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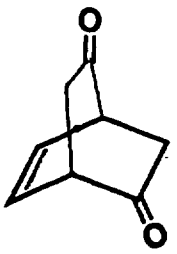
D. Nitrobarrelene Project

The known compounds 5,7-dioxo[2,2,2]bicyclooct-2-ene 1[1] and 2,6,7-trioxo[2,2,2]bicyclooctane 2[2] were prepared for investigations designed to provide nitro derivatives.



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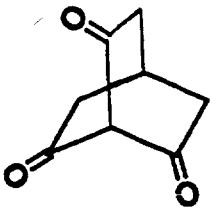
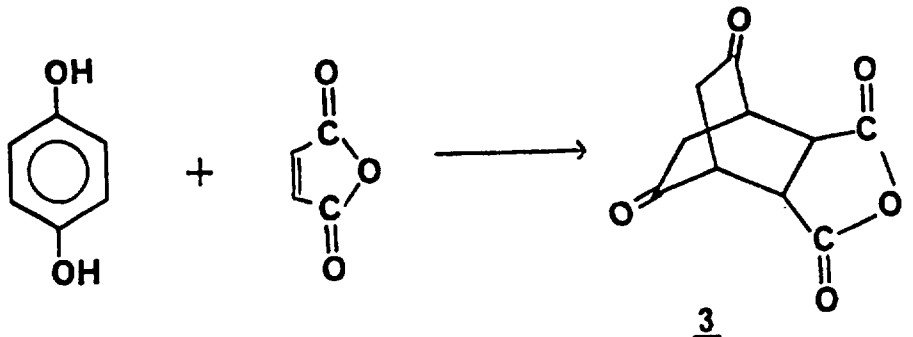


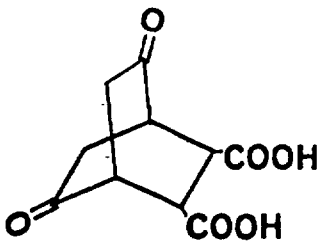
2

The diketoolefin 1 was obtained in three steps. Hydroquinone and maleic anhydride gave the Diels-Alder adduct 3 (14%), eq (1), Hydrolysis to the dicarboxylic acid 4 (66%) and oxidation by lead tetraacetate gave the product 1 (30%), eq (2).[1]



3

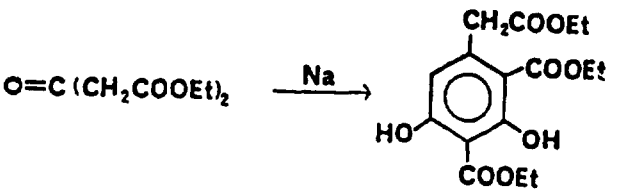
eq (1)



4

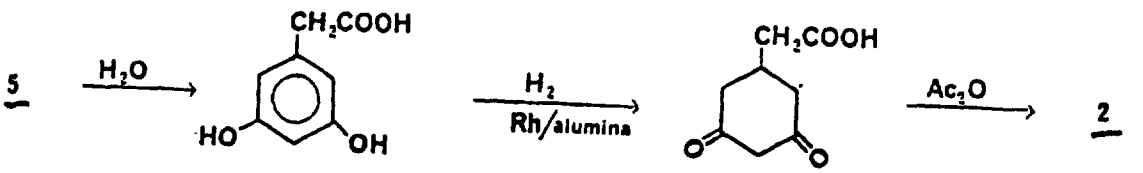
eq (2)

The triketone 2 was obtained in four steps. Diethyl 3-oxoadipate condensed with itself in the presence of sodium to the triester 5 (40%), eq (3). Hydrolysis and decarboxylation gave the acid 6 (40%). Reduction gave the diketoacid 7 (80%), and cyclization by treatment with acetic anhydride gave the product 2 (20%), eq (4).[2]



5

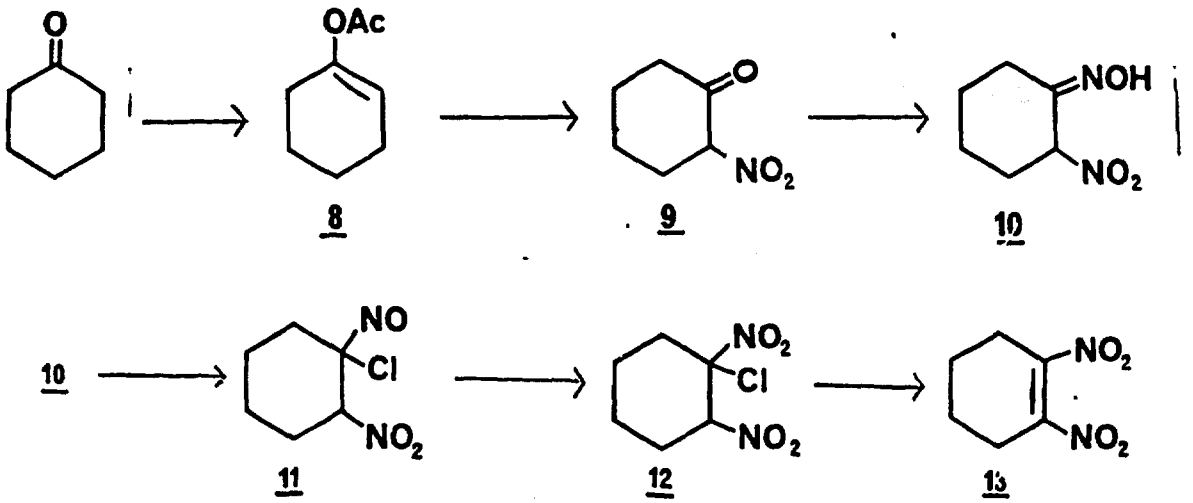
eq (3)



eq (4)

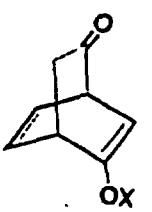
To establish models for eventual reactions in the bicyclic compounds the transformation of cyclohexanone to 1,2-dinitrocyclohexene 13, a previously unknown compound, was carried out. Isopropenyl acetate converted cyclohexanone to its enol acetate 8 (77%).[3] Nitration gave α-nitrocyclohexanone, 9 (60%),[3] and then treatment with hydroxylamine gave the oxime 10 (70%),[4] chlorine converted the oxime to the gem-chloronitroso compound 11 (%) which was oxidized by ozone to the chlorodinitrocyclohexane 12 (~40%).[5] Dehydrochlorination by treatment

with 1,5-diazabicyclo[5,4,0]undecane (DBU) afforded the dinitrocyclohexene 13, eq (5).



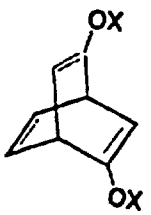
eq (5)

The diketoolefin 1 readily converted to the mono- and disilylenol ethers 14 and 16 on treatment with sodium ditrimethylsilylamine followed by trimethylsilyl chloride.[6] When the latter was replaced with acetyl chloride the monoenol acetate 15 was obtained. Attempts to prepare the dienol acetate 17 were unsuccessful.



14 X = $Si(CH_3)_3$

15 X = $COCH_3$

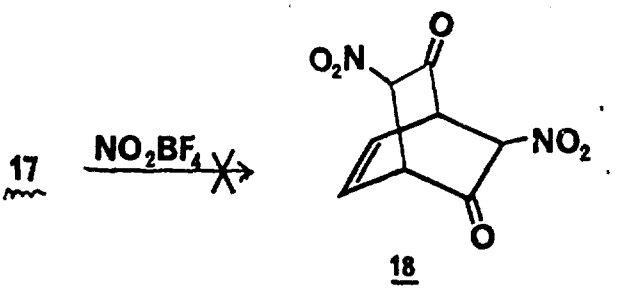


16 X = $Si(CH_3)_3$

17 X = $COCH_3$

Attempted nitration of the disilyl ether 16 by treatment with nitronium tetrafluoroborate gave a brown intractable resin; neither the anticipated mononitro compound nor the dinitro compound 18, eq (6) was detected.[7] Other schemes for nitration

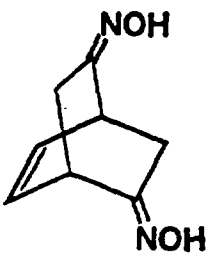
were also unsuccessful.



18

eq (6)

Conversions of ketones 1 and 2 to oxime derivatives 19 and 20 have been carried out. Product identification is not yet complete.



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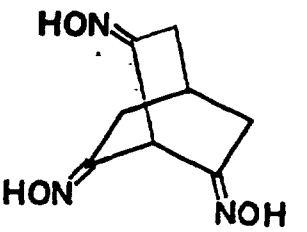
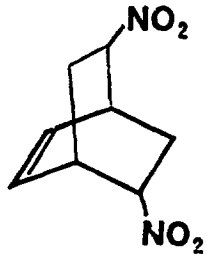


20

Further attempts will be made to nitrate the enol derivatives 14, 15, and 17.

Oxidation of oximes 19 and 20 to nitro compounds 21 and 22 and conversions of the oximes to nitro olefins 23 and 24 will be investigated. A typical anticipated route is shown, eq (7). The chemistry of the nitrovinyl units in 23 and 24 will be examined for conversion to hexanitrobarrelene 25 and the furoxan 26. The oxidation of the furoxan 26 to hexanitrobarrelene will be investigated.



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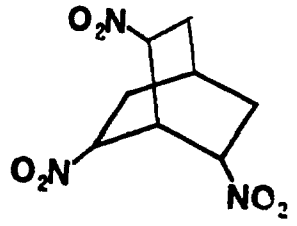

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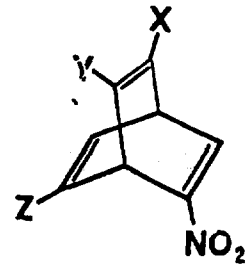
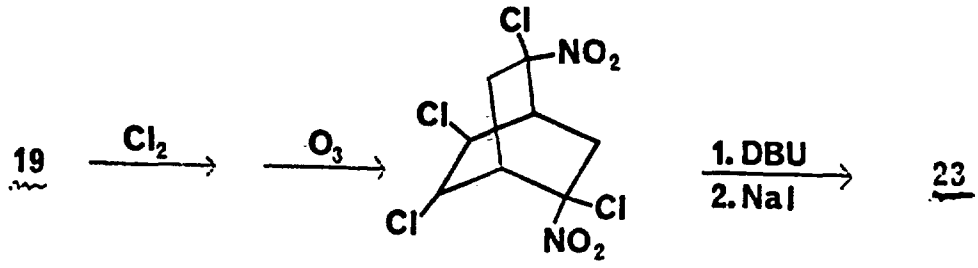
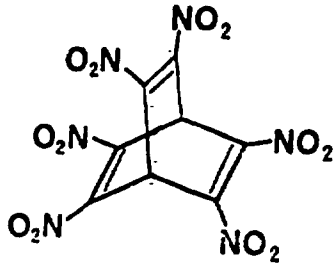


23 X = NO_2
Y = Z = H

24 X = H
Y = Z = NO_2



eq (7)



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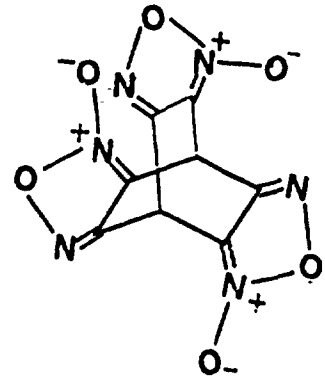

26

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E. Collaboration with NRL

Collaboration with Dr. M. D. Pace of the Naval Research Laboratory on the elucidation of electron transfer to give radical intermediates in the spontaneous conversion of N,N-dimethyl-2,4-dinitrobenzylamine to 6-nitro-2-methylindazole continued.

Samples of R-Salt and of the tetramethylcyanoisoxazoline-N-oxide (cpd 4 p 42) were submitted to Dr. Richard Gilardi for X-ray structure analysis.

F. The writing of a book, "The C-Nitro Derivatives of N- and N,O- Five-membered Heterocycles" was completed. The book will be published by VCH Publishers, Inc. (was Verlag Chemie International, Inc.) in 1985.

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