

Synthesis and Electron Spin Resonance of 3-Oxy-1,3-diazacyclohexene 1-Oxide (1,3-Nitrone–Nitroxide) Radicals

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Six-membered ring 1,3-nitrone–nitroxide radicals (3) possessing a potentially labile hydrogen atom have been obtained by oxidation of *NN'*-dihydroxy precursors (2), prepared in turn from an open-chain bishydroxylamine (1) and formaldehyde or acetaldehyde. Reaction between the bishydroxylamine and benzaldehyde produced a dinitrone (4). The nitrone–nitroxides have longer lifetimes than comparable simple α -unsubstituted nitroxides; the radical (3a) decomposes with first-order kinetics: $k_{e.s.r.} = 6 \times 10^{-4} \text{ s}^{-1}$ in benzene at 25 °C.

FREE radicals, when used as spin-labels,¹ must undergo chemical transformations without loss of paramagnetism. Such reactions on stable nitroxide radicals cannot be performed at positions α to the nitroxide group, because these positions are substituted, usually with methyl groups, to prevent decomposition by loss of an α -hydrogen atom.² The nitrone–nitroxides (5) however exhibit chemical versatility at the 2-position, which is α to both nitrogen atoms. Chemical changes at this position or in the immediate side-chain affect the e.s.r. spectra, and this has found application in problems of structure and mechanism.^{3,4} Resonance stabilisation by the nitrone–nitroxide system might be expected to result in usefully long lifetimes for free radicals of the form (3) in which a second α -position is not fully substituted. We have prepared and studied compounds of this type.

2-Methyl-2,4-dinitropentane was reduced with zinc and ammonium chloride to the bishydroxylamine (1). This was susceptible to aerial oxidation, and was condensed, without isolation, with aldehydes to obtain the cyclic radical precursors (2). Since the product

(2b) from acetaldehyde was a diastereoisomeric mixture, the structure was confirmed by n.m.r. and by the e.s.r. spectrum of the derived radical.

When the bishydroxylamine was condensed with benzaldehyde, the product was a dinitrone (4). The absorption spectra were typical of a nitrone system.⁵ The intensity of u.v. absorption necessitated two nitrone groups and, in agreement with this, the n.m.r. integration showed that a multiplet of the aromatic protons obscured a signal for two additional protons (τ 2.6) in a region predicted for the system $\text{N}^+(\text{O}^-)\text{CHAr}$.⁶ The compound is therefore produced by the more common reaction between an *N*-substituted hydroxyamino-group and an aldehyde, without cyclisation. Its formation requires two molecules of benzaldehyde, but no other product was obtained by varying the molar ratio. It has already been reported that the formation of five-membered cyclic nitrone–nitroxide precursors by the reaction between a bishydroxylamine and aromatic aldehydes is slow.³

Oxidation of the radical precursors (2) with lead

³ E. F. Ullman, J. H. Osiecki, D. G. B. Boocock, and R. Darcy, *J. Amer. Chem. Soc.*, 1972, **94**, 7049.

⁴ E. F. Ullman and R. Darcy, *J. Amer. Chem. Soc.*, 1971, **91**, 1024.

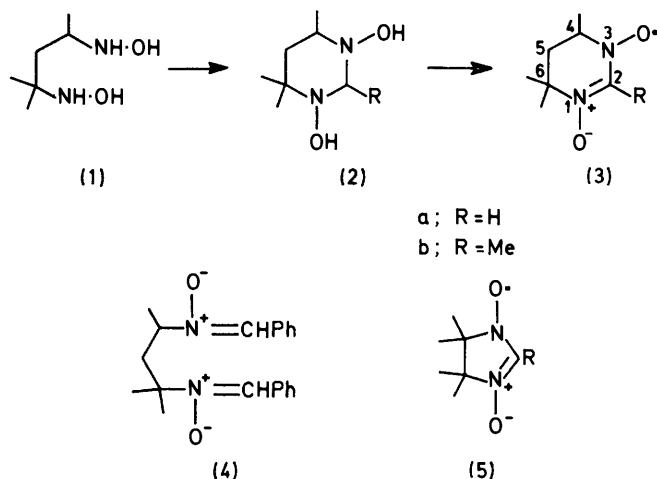
⁵ J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473; G. R. Delpierre and M. Lamchen, *Quart. Rev.*, 1965, **19**, 329.

⁶ K. Koyano and H. Suzuki, *Tetrahedron Letters*, 1968, 1859.

¹ 'Spin Labelling, Theory and Applications,' ed. L. J. Berliner, Academic Press, New York, 1975.

² A. R. Forrester, J. M. Hay, and R. H. Thomson, 'Organic Chemistry of Stable Free Radicals,' Academic Press, London, 1968, p. 193.

dioxide afforded the nitrono-nitroxides (3), which are red or blue in solution depending on whether the solvent is polar or non-polar. The radicals decompose within hours in solution, and could not be isolated. They are significantly more stable than comparable α -unsubstituted nitroxides,⁷ and it was possible to measure decomposition rates by routine scanning of the e.s.r. spectra. The nitrono-nitroxide (3a) decomposes with first-order



kinetics ($k_{e.s.r.} 6 \times 10^{-4} \text{ s}^{-1}$ at 25 °C) in the concentration range 5×10^{-5} – $2 \times 10^{-4} \text{ M}$. α -Methine nitroxides decompose with second-order kinetics, by transfer of a hydrogen atom to a second radical molecule.⁷ It has been demonstrated⁸ that if slow decay of the e.s.r. signal is observed for a radical which is in rapid equilibrium with its dimer, the measured rate ($k_{e.s.r.}$) will show first-order behaviour. This applies whether decomposition involves slow bimolecular disproportionation of the monomer or slow unimolecular decomposition of the dimer. The e.s.r. spectrum of the nitrono-nitroxide (3a) was unaffected by varying the temperature in the range 10–40 °C, which discounts the presence of dimer. Decomposition may take place by intramolecular transfer of a hydrogen atom from carbon (C-4) to the I-oxygen, producing a reactive carbon radical. The decomposition and other reactions are being studied.

The e.s.r. spectra of the radicals (see Table) are consistent with hyperfine coupling by two virtually equivalent nitrogen nuclei, with further splitting where possible

E.s.r. data for the nitrono-nitroxides (3) in benzene

| Compound | $a_N(\text{G})$ | a_R | a_{H-4} | g |
|----------|-----------------|-------|-----------|----------|
| (3a) | 6.9 | 3.8 | 10.9 | 2.006 62 |
| (3b) | 6.8 | 3.3 | 10.6 | 2.006 65 |

by ring- and 2-methyl-hydrogen nuclei. The nitrogen coupling constant is less than for five-membered cyclic

nitrono-nitroxides³ [for (5; R = Me), $a_N = 7.4$], except where these have strongly electron-withdrawing substituents. Considering the electron-withdrawing effect of the nitrono group on the nitroxide group, then according to Walter's principle⁹ that the electron pair is preferentially delocalised by an electron-withdrawing substituent, the form >N-O with the lone pair on nitrogen is stabilised relative to the other form (>N-O^-) and makes a greater contribution to the resonance structure. The value of a_N is therefore decreased by increased conjugation between the nitrono and nitroxide groups in the six-membered ring.

Hyperfine coupling by H-2 is not observed in deuterium oxide and base where the nitrono-nitroxide system forms the radical anion by loss of this proton.¹⁰ The larger coupling is due to H-4, which interacts with the unpaired electron by hyperconjugation. From the relationship¹¹ $a_{H-4} = B \cos^{20} \rho_N$, the value of the dihedral angle between the C-H bond and the nitrogen π -orbital in the radical (3a) emerges as 10°. This is consistent with H-4 having the pseudo-axial conformation, with two of the three methyl groups pseudo-equatorial. Conformation therefore causes a_{H-4} to have the large value of 10.9 G, which is not significantly different from that (11.7 G) for the α -hydrogen atoms in the very unstable piperidino-oxyl.¹² The value of a_N is however much smaller (6.9 G; cf. 17.4 G for piperidino-oxyl) because of conjugation, and reflects the lesser tendency of the nitrono-nitroxide to form a C=N bond by losing the α -hydrogen atom.

EXPERIMENTAL

E.s.r. spectra were recorded by using a Decca X-1 spectrometer operating at 9.3 GHz, with 100 kHz modulation. The g values ($\pm 0.000 05$) were measured by using Mn^{II} in magnesium oxide as reference (separation of lines 3 and 4 = 86.8 G), with diphenylpicrylhydrazyl ($g = 2.003 6$, powder) as primary standard. The rate constant ($\pm 0.5 \times 10^{-4} \text{ s}^{-1}$) was measured by observing the decay of the e.s.r. spectrum at 5 min intervals.

4,4,6-Trimethylperhydropyrimidine-1,3-diol (2a).—2-Methyl-2,4-dinitropentane¹³ (8.8 g) was suspended in a solution of ammonium chloride (5 g) in 50% v/v water-ethanol (100 ml), cooled below 5 °C. Activated zinc dust¹⁴ (20 g) was added with stirring, at 0–5 °C, over 2 h. After 30 min, formaldehyde (40%; 7.5 ml) was added dropwise with continued cooling. After a further 2 h the mixture was allowed to come to room temperature, and stirred overnight. Solid was filtered off and washed with hot ethanol. The filtrate and washings were evaporated under reduced pressure, and the residual oil dried in a vacuum desiccator, redissolved in chloroform to permit drying with anhydrous sodium sulphate, and finally crystallised from chloroform-ether to give the *bishydroxylamine* (2a) (1.2 g), m.p. 156° (Found: C, 52.65; H, 10.15;

⁷ D. F. Bowman, T. Gillan, and K. U. Ingold, *J. Amer. Chem. Soc.*, 1971, **93**, 6555.

⁸ S. A. Weiner and L. R. Mahoney, *J. Amer. Chem. Soc.*, 1972, **94**, 5029.

⁹ R. I. Walter, *J. Amer. Chem. Soc.*, 1966, **88**, 1923.

¹⁰ D. G. B. Boocock, R. Darcy, and E. F. Ullman, *J. Amer. Chem. Soc.*, 1968, **90**, 5945.

¹¹ E. G. Janzen, *Topics Stereochem.*, 1971, **6**, 177.

¹² G. M. Coppinger and J. D. Swalen, *J. Amer. Chem. Soc.*, 1961, **83**, 4900.

¹³ G. L. Shoemaker and R. W. Keown, *J. Amer. Chem. Soc.*, 1954, **76**, 6374.

¹⁴ L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1968, p. 1276.

N, 17.7. $C_7H_{16}N_2O_2$ requires C, 52.45; H, 10.05; N, 17.5%; ν_{\max} . (KBr) 3 230 cm^{-1} (OH); τ ($CDCl_3$) 5.9 (2 H, q, J 11 Hz, $N\cdot CH_2\cdot N$), 7.0 (1 H, m, CH), 8.4 (2 H, m, $C\cdot CH_2\cdot C$), and 8.8 (9 H, m, 3 CH_3).

Reaction of Reduced 2-Methyl-2,4-dinitropentane with Benzaldehyde.—2-Methyl-2,4-dinitropentane (4.4 g) was reduced with zinc dust in ammonium chloride solution as described above. Benzaldehyde (5.3 g) was added to the mixture, which was allowed to come slowly to room temperature and stirred overnight. The solution was filtered and the solid washed with hot ethanol. Filtrate and washings were evaporated to an oil, which was redissolved in chloroform and dried with anhydrous sodium sulphate. The cream-coloured product, *NN'*-dibenzylidene-2-methyl-pentane-2,4-diamine *NN'*-dioxide (5 g) crystallised from ether-petroleum (b.p. 40—60 °C); m.p. 115° (Found: C, 74.45; H, 7.65; N, 8.75. $C_{20}H_{24}N_2O_2$ requires C, 74.45;

H, 7.45; N, 8.65%); ν_{\max} . ($CHCl_3$) 1 580, 1 560, and 1 100—1 180 cm^{-1} ($C:N^+\cdot O^-$); τ ($CDCl_3$) 1.75 (4 H, m, ArH), 2.6 (8 H, m, ArH and $2 \times N:CHAr$), 5.7 (1 H, m, CH), 7.5 (2 H, m, CH_2), and 8.45 (9 H, m, 3 CH_3); λ_{\max} . (EtOH) 224 (ϵ 11 100), 230sh (10 100), 288 (28 300), and 305sh nm (19 100).

3,4,5,6-Tetrahydro-4,6,6-trimethyl-3-oxypyrimidine 1-Oxide (3a).—The bishydroxylamine (2a) (7 mg) in benzene (10 ml) was stirred while lead dioxide (100 mg) was added. Stirring was continued for 30 s, then the lead dioxide was removed by centrifugation. 3,4,5,6-Tetrahydro-2,4,6,6-tetramethyl-3-oxypyrimidine 1-oxide (3b) was similarly prepared.

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