A New Group of Nitroxide Free Radicals formed from Aliphatic Nitrosamines and Thiols

By WILLIAM A. WATERS

(*Dyson Perrins Laboratory, Oxford University, South Parks Rd., Oxford* OX1 3QY)

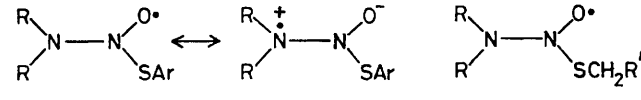
Summary Two simple nitrosamines react under nitrogen with typical thiols to give minute concentrations of free radicals which, from their e.s.r. spectra, are assigned the structure $R_2NN(O\cdot)SR'$.

NITROXIDE radicals derived from aliphatic nitrosamines, R_2NNO, have not been described hitherto. Attempts to make radicals $R_2NNHO\cdot$ by 1-electron reduction [equation (1)] fail owing to the ease of release of nitric oxide[1,2] but I

$$R_2NNO + Fe^{II}(Cu^{I}) + H^{+} \longrightarrow R_2NH + NO + Fe^{III}(Cu^{II}) \quad (1)$$

have found by e.s.r. spectroscopy that under nitrogen both *N*-nitrosopiperidine and *N*-nitrosodiethylamine react with typical thiols to give low concentrations of radicals, the spectra of which have the surprisingly high g value of $2{\cdot}029 \pm 0{\cdot}002$; in a Varian E4 spectrometer they appear at *ca.* 40 G to the low field side of the spectrum of Frémy's salt.

The first spectrum to be discovered was obtained from concentrated mixtures (*ca.* 1—2 M of each) of nitrosopiperidine and 4-methylthiophenol in benzene and had 5 weak, broad lines with relative intensities 1:2:3:2:1. It was detectable in a few minutes after admixture, strengthened gradually during *ca.* 30 min and thereafter persisted for several hours but weakened to a single broad line on allowing access of air to the sample. Identical spectra were obtained from ethanolic solutions. The aliphatic thiols, RCH_2SH, which were only studied in aqueous ethanol gave weaker spectra, detectable only at high receiver gain ($2{\cdot}5$—$4{\cdot}0 \times 10^3$) and with difficulty could be partly resolved into 11 evenly spaced lines, so corresponding to radicals in which $a(CH_2)$ is about half $a(N_1)$ or $a(N_2)$.



(I) (II)

These e.s.r. spectra correspond to radicals (I) and (II) (Table) in both of which part of the unpaired electron spin density is divided almost equally between the two nitrogen atoms and the remainder located to a significant extent on the sulphur atom; postulation of a high electron spin

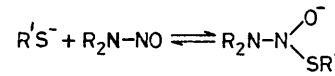
density on sulphur helps to explain the high g values of all these spectra.

TABLE. Splitting constants (mT) and g values of radicals (I) and (II).[a]

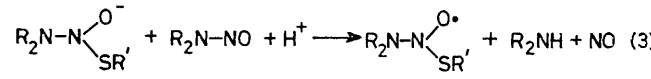
Thiol	*N*-Nitrosopiperidine			*N*-Nitrosodiethylamine		
	a(N)	a(CH_2)	g	a(N)	a(CH_2)	g
PhSH	0·250	—	—	0·244	—	2·028
p-MeC_6H_4SH	0·255	—	2·029	0·242	—	2·028
$HSCH_2CH_2OH$	0·257	0·130	2·029	0·260	0·13	2·030
$HSCH_2CO_2K$	0·255	0·131	2·029	0·264	0·131	2·029
L-Cysteine	Not resolvable		2·030	0·26	0·13	2·030

[a] The average errors for the splitting constants are 0·005 mT. The line width (peak–peak) for the radicals (I) is *ca.* 0·13 mT.

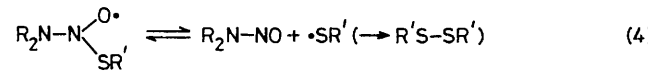
With the aliphatic thiols the best spectra were obtained in alkaline solutions (pH 8—11), though their intensities did not increase more than 4-fold for a 10^4 variation of [OH^-]; an even smaller variation was noticed with the aromatic thiols. No spectrum could be obtained by the use of free thioglycollic acid. Unchanged nitrosamine and thiol both remained for some days in each reaction mixture. Since the signal strengths indicate that the radical concentrations are at most 10^{-6} of those of the components it seems that they have been formed by very slow reactions which either involve unfavourable reversible equilibria or are followed by an irreversible decomposition (*cf.* reaction between *C*-nitroso-compounds and olefins[3]). Consequently, the mechanism shown in reactions (2)—(4) is suggested tentatively.



(2)



(3)



(4)

Reaction (4) is somewhat analogous to that of the recently studied[4] decomposition of the pink adducts of thiols to sodium nitroprusside. No evidence has been found for the elimination of thionitrites, which can occur when *N*-nitrosoamides are treated with thiols[5] [reaction (5)].

$$ArSO_2\text{–}N(NO)Me + R'SH \longrightarrow ArSO_2\text{–}NHMe + R'S\text{–}NO \quad (5)$$

These reactions may be cogent in explaining the carcinogenicity of dialkyl nitrosamines in view of the ready reactions between polycyclic aromatic hydrocarbons and thiyl radicals[6] which could explain the initial binding of carcinogenic hydrocarbons *in vivo*. From the nitrosamines however the reductive formation of nitric oxide *in vivo* by reaction (1) has more obvious toxicological implications.

(*Received, 24th May* 1978; *Com.* 552.)

[1] K. Lehmstedt, *Ber.*, 1927, **60**, 1910.
[2] E. C. S. Jones and J. Kenner, *J. Chem. Soc.*, 1932, 711.
[3] D. Mulvey and W. A. Waters, *J.C.S. Perkin II*, 1978, in the press.
[4] D. Mulvey and W. A. Waters, *J.C.S. Dalton*, 1975, 951.
[5] U. Schulz and D. R. McCalla, *Canad. J. Chem.*, 1969, **47**, 2021.
[6] A. L. J. Beckwith and B. S. Low, *J. Chem. Soc.*, 1961, 1304; *Austral. J. Chem.*, 1963, **16**, 845; 1964, **17**, 108.