Electron Spin Resonance Studies of Spin Trapping. On the Role of Hydroxylamines and an Oxaziridine in the Formation of Nitroxides following Addition of Hydroxyalkyl Radicals to *N*-t-Butyl-α-phenylnitrone

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E.s.r. experiments demonstrate that when α-hydroxyalkyl radicals $\cdot CR^1R^2OH$ are generated photochemically in the presence of the nitrone $PhCH{=}N^+(Bu^t)O^-$ the resulting adducts $PhCH(CR^1R^2OH)N(Bu^t)O\cdot$ are photochemically labile but build up with time when irradiation is interrupted. The latter unusual observation is interpreted in terms of the oxidation of the intermediate hydroxylamine (generated by photolysis of the nitroxide) by the oxaziridine, $\mathrm{Ph}\overline{\mathrm{CH{\cdot}NBu^{t}{\cdot}O}}$, which results from photolysis of thet rap. These findings, and the results obtained when oxygen is admitted, point to the need for caution in interpreting results from spin-trapping experiments.

CONSIDERABLE use has recently been made of the ability of nitrones to react with transient radicals to form longer-lived nitroxides, a process commonly referred to as 'spin trapping'.[1,2] E.s.r. spectra of the resulting spin-adducts can often provide valuable information concerning the structure of the intermediate radicals and the mechanisms of the reactions in which they are involved, though cautionary notes have been sounded (see *e.g.* ref. 3) concerning valid mechanistic interpretation.

We have investigated the formation and reaction of photochemically generated α-hydroxyalkyl radicals (1) in the presence of the most commonly encountered nitrone spin-trap, *N*-t-butyl-α-phenylnitrone (2). The main interest attaches not to the e.s.r. parameters themselves but to the complex sequence of events involved in the generation of the radicals detected. Our observations, which we believe have a general significance for the interpretation of spin-trapping results, refer to the thermochemical processes which occur when u.v. irradiation is stopped, as well as to photochemical processes occurring during irradiation, to the effect of repeated cycles of this type, and also to the effect of oxygen.

$$R^1R^2\dot{C}OH \quad \begin{array}{l} a;\ R^1 = R^2 = H \\ b;\ R^1 = H,\ R^2 = Me \\ c;\ R^1 = R^2 = Me \\ d;\ R^1 = Me,\ R^2 = Ph \end{array}$$

(1)

$$PhCH{=}N^+(Bu^t)O^-$$

(2)

RESULTS AND DISCUSSION

E.S.R. Observations.—Hydroxyalkyl radicals were generated *in situ* by photolysis of the appropriate ketone in solvents capable of donating a hydrogen atom;[4,5] in some cases this was the corresponding alcohol so that both ketone and alcohol produced the same radical [*cf.* reactions (1) and (2)]. Attack of t-butoxyl radicals (generated from photolysis of di-t-butyl peroxide) on the parent alcohol was also employed.

Experiments in the absence of trap led simply to the detection of signals from the appropriate radicals[4,5] (1), the spectra of which will not be discussed here. Experiments in the presence of the spin trap (2) gave complex results, of which a typical set is as follows.

$$R^1R^2CO \xrightarrow[h\nu]{RH} R^1R^2\dot{C}OH \xleftarrow{Bu^tO\cdot} R^1R^2CHOH \qquad (1)$$

$$R^1R^2CO + R^1R^2CHOH \xrightarrow{h\nu} 2R^1R^2\dot{C}OH \qquad (2)$$

Irradiation of a degassed solution of acetone in methylcyclopentane at *ca.* 0 °C with light from a focused 1 000-W mercury–xenon lamp in the presence of (2) resulted in the detection of two nitroxides, designated (A) and (B). The former, with g 2.006 27, a(N) 1.35, a(1 H) 0.17 mT, appeared when the sample was exposed to irradiation for a short time (*ca.* 2 s); it was also formed when a solution of (2) alone in methylcyclopentane was similarly photolysed. While this nitroxide only slowly decomposed in the absence of light, further irradiation (*ca.* 2—3 s) effected its destruction. During the initial build-up and destruction of (A), a weak signal from (B) [with g 2.0060, a(N) 1.51, a(1 H) 0.36 mT] was observed; in the absence of light its intensity markedly increased. This signal was allowed to build up (for *ca.* 8 h) and was found to be stable in the absence of light but, on re-focusing the light source on the sample, the signal was immediately reduced in intensity. On removal of the light source the intensity of the signal from radical (B) again increased in intensity. When the sequence was repeated several times, until (2) was expended, signals from both 1-hydroxy-1-methylethyl radicals (1c)[5] and radical (B) were observed. With the removal of the light source, the signal from the radical (1c) disappeared and the signal from radical (B) increased in intensity.

The build-up of radical (B) in the dark after an initial burst of irradiation (say 10 s) was observed not only when (1c) was produced by photoreduction of the ketone in the presence of (2) but also when it was formed from propan-2-ol by hydrogen abstraction by t-butoxyl.

On introducing air to a sample containing the nitroxide (B) and shaking the mixture, the signals from (B) broadened somewhat. On re-focusing the light source there was, first, an instantaneous build up of radical (B), followed by an equally rapid decrease in the concentration of the radical, the overall sequence requiring only a few seconds.

The e.s.r. parameters of the nitroxide (A) produced after a momentary exposure of (2) and methylcyclopentane, or (2), acetone, and methylcyclopentane to light are consistent with this species being a spin-adduct of an alkoxyl radical and (2), *i.e.* (3).[6-9] Its formation is thought to result from trace impurities of peroxide in the solvent, which on photolysis produce alkoxyl radicals which react with the trap. The radical-adduct (3) is itself evidently photolabile and decomposes on further irradiation.

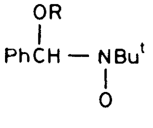
The behaviour described here for photolysis of solutions which we expect to generate $\cdot CMe_2OH$ (1c) was also shown in experiments in which other hydroxyalkyl radicals, including hydroxymethyl (1a), 1-hydroxyethyl (1b), and 1-hydroxy-1-phenylethyl (1d) were generated from methanol, ethanol, and 1-phenylethanol, respectively [and also for (1d) from photoreduction of acetophenone in methylcyclopentane or cyclopropane containing 1-phenylethanol]. The e.s.r. parameters of corresponding nitroxide radicals of type (B) (see Table) are of a magnitude anticipated for the radicals (4) formed by reaction of first-formed hydroxyalkyl radicals with (2) (*cf.* ref. 10) and serve to identify these adducts.

E.s.r. parameters of nitroxides generated by reaction of α-hydroxyalkyl radicals with (2)

Radical	g [a]	Hyperfine splittings (mT) [b]		g [a]	Hyperfine splittings (mT)	
		a(N)	a(H)		a(N)	a(H)
	(in cyclopropane)			(in methylcyclopentane)		
(4a)	2.0058	1.53	0.36	2.0060	1.50	0.40
(4b)	2.0060	1.54	0.33	2.0060	1.51	0.37
(4c)	2.0060	1.52	0.35	2.0060	1.51	0.36
(4d)	2.0060	1.47	0.31	2.0061	1.45	0.29

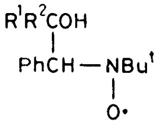
[a] ±0.0001. [b] ±0.01 mT.

Mechanistic Implications.—The important observation for which an explanation must be sought is the significant and steady increase in concentration of radicals (4) when the irradiation was terminated. This implies that the radicals are generated by a *thermal* reaction, evidently involving one (or more) non-radical species generated during the photolysis.



$$\begin{array}{c} OR \\ | \\ PhCH-NBu^t \\ | \\ O \end{array}$$

(3)

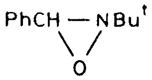


$$\begin{array}{c} R^1R^2COH \\ | \\ PhCH-NBu^t \\ | \\ O\cdot \end{array}$$

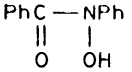
(4)

Several observations concerning the reactivity of nitrones and nitroxides may well be relevant. Thus, while it is well known that (2), and nitrones in general, undergo photochemical isomerisation to oxaziridines,[11,12] it is perhaps not generally recognized that oxaziridines are capable of oxidising hydroxylamines to nitroxides. For example,[13] 2-t-butyl-3-phenyloxaziridine (5) reacts with *N*-benzoyl-*N*-phenylhydroxylamine (6) in the dark to give the benzoyl nitroxide (7).

Further, while nitroxides are relatively stable in the absence of light, they are sensitive to light, and are in photoequilibrium with hydroxylamines.[12] Nitroxides and hydroxylamines also undergo ready hydrogen exchange,[14] and it is possible that an excited nitroxide dimerises to give a 'neutral dimer' which can then thermally reorganise to the hydroxylamine.[15,16]

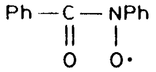


(5)



$$\begin{array}{cc} PhC & -NPh \\ \| & | \\ O & OH \end{array}$$

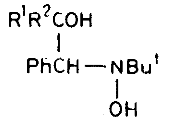
(6)



$$\begin{array}{ccc} Ph- & C & -NPh \\ & \| & | \\ & O & O\cdot \end{array}$$

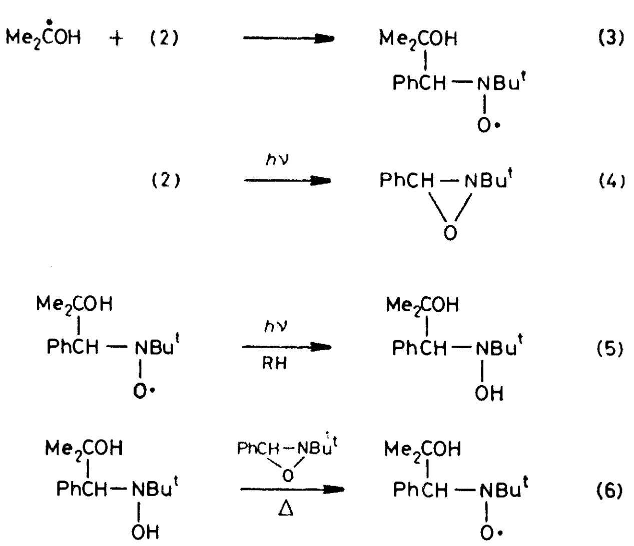
(7)

Here, the hydroxyalkyl radicals produced by photoreduction of ketone or hydrogen abstraction from alcohol are thought to react with (2) to produce the nitroxide radicals (4), which themselves must be photochemically labile, presumably abstracting a further hydrogen atom (*e.g.* from alcohol) to give the hydroxylamines (8). By analogy with the reaction of (5) and (6) to give (7), we suggest that the oxaziridine (5), formed by photochemically induced isomerisation of (2), a process in competition with the reaction of (2) with radicals (1), oxidises the hydroxylamine (8) to the nitroxide (4) [see *e.g.* reactions (3)—(6)]. This sequence would continue after the light source had been removed and would account for the increase in concentration with time of nitroxides (8) which is observed under these conditions.

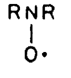


$$\begin{array}{c} R^1R^2COH \\ | \\ PhCH-NBu^t \\ | \\ OH \end{array}$$

(8)



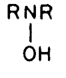
Further Experiments.—Additional experiments substantiated the key features of the proposed mechanism. First, di-t-butyl nitroxide (9a) was found to be stable in solution (*e.g.* in both methylcyclopentane and methylcyclopentane–propan-2-ol mixtures), but its e.s.r. signal decayed fairly quickly on irradiation. It is believed that the photochemically excited nitroxide is converted into di-t-butylhydroxylamine (10a) [*cf.* reaction (5)] and this is in keeping with the observation that its decay was slower in cyclopropane or benzene than in methylcyclopentane (from which hydrogen abstraction would be expected to be more facile). Secondly, a solution of diethylhydroxylamine (10b) in methylcyclopentane was found to be stable towards (2) in the absence of oxygen, but to react readily to form the corresponding nitroxide (9b)[16] on addition of a solution of (2) in methylcyclopentane which had been irradiated for 10 s. In a control experiment, no nitroxides were detected when methylcyclopentane which had been irradiated was added to diethylhydroxylamine. These results confirm that it is a diamagnetic photoproduct of (2) which is responsible for the oxidation of the hydroxylamine.



$$\begin{array}{c}\mathrm{RNR}\\ |\\ \mathrm{O\cdot}\end{array}$$

(9)

a; R = $\mathrm{Bu^t}$
b; R = Et



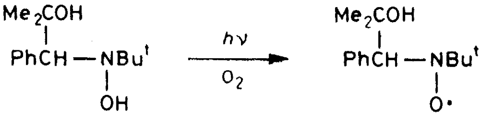
$$\begin{array}{c}\mathrm{RNR}\\ |\\ \mathrm{OH}\end{array}$$

(10)

a; R = $\mathrm{Bu^t}$
b; R = Et

Finally, that the key photoproduct is the oxaziridine (5) is suggested by our finding that irradiation of (2) in methylcyclopentane at 254 nm for 2 h yields only (5), in addition to unchanged starting material, and, further, that a synthetic sample of this oxaziridine readily oxidizes diethylhydroxylamine to the corresponding nitroxide [*cf.* reaction (6)]. The mechanism of this type of reaction is now being studied further.

The instantaneous build up of radical (B) on refocusing the light in a reaction mixture to which a limited amount of oxygen has been added is then interpreted in terms of the oxidation by molecular oxygen of hydroxylamine formed from the nitroxide during photolysis [reaction (7); *cf.* an earlier report[16] of the oxidation of diethylhydroxylamine under similar conditions]. The subsequent equally rapid decrease in the concentration of the nitroxide, as the dissolved oxygen is used up, results in formation of hydroxylamine. The sequence is then evidently repeated when the sample is shaken again with air.



$$\begin{array}{c}\mathrm{Me_2COH}\\ |\\ \mathrm{PhCH{-}NBu^t}\\ \quad\ |\\ \quad\ \mathrm{OH}\end{array} \xrightarrow[\mathrm{O_2}]{h\nu} \begin{array}{c}\mathrm{Me_2COH}\\ |\\ \mathrm{PhCH{-}NBu^t}\\ \quad\ |\\ \quad\ \mathrm{O\cdot}\end{array} \qquad (7)$$

Conclusion.—The experiments reported here, and the sequence shown in detail for the reaction of the 1-hydroxy-1-methylethyl radical [reactions (3)—(6)] with the nitrone spin trap (2), demonstrate a complexity in the spin-trapping reaction of hydroxyalkyl radicals with (2) that was not anticipated. This points to the need for caution in interpreting trapping reactions and highlights the important roles which can be played by the diamagnetic materials present.

EXPERIMENTAL

(i) *E.S.R. Experiments.*—The e.s.r. spectra were measured on a Varian E-104 X-band spectrometer employing 100-kHz modulation. Details of the procedure for measuring and calibrating spectra and the photolytic apparatus have been described previously.[17] Solutions to be photolysed contained spin trap (2) (*ca.* 3—5 mg) in one of the following mixtures: ketone (*ca.* 0.15 ml) and methylcyclopentane (1.3 ml); ketone (*ca.* 0.15 ml) and methylcyclopentane–alcohol mixtures (1.3 ml; *ca.* 10 : 1); ketone and cyclopropane (1 : 10); ketone, alcohol, and cyclopropane (1 : 1 : 10); alcohol, di-t-butyl peroxide, and solvent (1 : 2 : 10). All solvents and reagents, except where otherwise stated, were commercially available. Solutions were deaerated by a vacuum-freezing technique.

(ii) *Product Studies.*—A degassed solution of *N*-t-butyl-α-phenylnitrone (2) in AnalaR benzene (5 $\mathrm{cm^3}$) in a silica container was irradiated in a Rayonet photochemical reactor (254 nm) for 2 h. Isolation of the product gave a mixture (1 : 2) of starting *N*-oxide and 2-t-butyl-3-phenyloxaziridine identical to an authentic sample;[18] δ_H 1.08 (9 H, $\mathrm{Bu^t}$), 4.62 (1 H, CH), and 7.28 (5 H, aromatic), δ_C 25.2 ($\mathrm{CH_3}$), 58.2 (C-3), 73.5 (C-2), and 127.5, 128.3, 129.6, and 135.7 p.p.m. (aromatic) (Found: C, 73.8; H, 8.5; N, 8.0. Calc. for $\mathrm{C_{11}H_{15}NO}$: C, 74.5; H, 8.5; N, 7.9%).

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REFERENCES

[1] E. G. Janzen, *Acc. Chem. Res.*, 1971, **4**, 31.
[2] ' Organic Free Radicals ', ed. W. A. Pryor, A.C.S. Symposium Series 69, Am. Chem. Soc., Washington, D.C., 1978, p. 433.
[3] A. R. Forrester and S. P. Hepburn, *J. Chem. Soc. (C)*, 1971, 701.
[4] H. Paul and H. Fischer, *Chem. Commun.*, 1971, 1038.
[5] R. Livingston and H. Zeldes, *J. Chem. Phys.*, 1966, **44**, 1245.
[6] M. V. Merritt and R. A. Johnson, *J. Am. Chem. Soc.*, 1977, **99**, 3713.
[7] J. A. Howard and J. C. Tait, *Can. J. Chem.*, 1978, **56**, 176.
[8] E. G. Janzen, D. E. Nutter, E. R. Davis, B. J. Blackburn, J. L. Poyer, and P. B. McCay, *Can. J. Chem.*, 1978, **56**, 2237.
[9] N. Ohto, E. Niki, and Y. Kamiya, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1770.
[10] Y. Kotake, K. Kuwata, and E. G. Janzen, *J. Phys. Chem.*, 1979, **83**, 3024.
[11] D. St.C. Black, N. A. Blackman, and L. M. Johnstone, *Aust. J. Chem.*, 1979, **32**, 2041.
[12] D. St.C. Black, N. A. Blackman, and A. B. Boscacci, *Aust. J. Chem.*, 1979, **32**, 1775.
[13] A. L. Bluhm and J. Weinstein, *J. Am. Chem. Soc.*, 1970, **92**, 1444.
[14] M. A. Schwartz, J. W. Parce, and H. M. McConnell, *J. Am. Chem. Soc.*, 1979, **101**, 3592.
[15] K. Adamic, D. F. Bowman, and K. U. Ingold, *J. Am. Chem. Soc.*, 1970, **92**, 1093.
[16] K. Adamic, D. F. Bowman, T. Gillan, and K. U. Ingold, *J. Am. Chem. Soc.*, 1971, **93**, 902.
[17] C. Gaze and B. C. Gilbert, *J. Chem. Soc. Perkin Trans. 2*, 1977, 116.
[18] W. D. Emmons, *J. Am. Chem. Soc.*, 1957, **79**, 5739.