Thermal Elimination Reactions of Nitrones. Part 1. Applications, Limitations, and Stereochemistry

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A series of N-(fluoren-9-ylidene)alkylamine N-oxides has been synthesised by direct oxidation of the parent imines with peroxy-acid. Most of these nitrones underwent a thermal elimination reaction (analogous to the Cope elimination of tertiary amine oxides) to produce olefin and oxime products. The elimination reaction was followed by g.l.c. and mass and n.m.r. spectroscopic techniques, and the results are rationalised in terms of several factors including statistical and steric effects and olefin stability. The applications and limitations of this nitrone elimination reaction and the relationship between the stereochemistry of reactants and that of products has been examined for various nitrones $R^1R^2C=N^+(O^-)R^3$ (R^1 = aryl, R^2 = H; R^1 and R^2 both alkyl; R^1 = alkyl, R^2 = aryl; R^1 and R^2 both aryl).

THE N-oxides of amines differ from those of imines (nitrones) in having tetrahedral and trigonal nitrogen configurations, respectively. Further differences are found in their thermal reactions: tertiary amine oxides upon heating decompose to form hydroxylamines and olefins (Cope elimination [1]), whereas nitrones are reported [2] to give different types of products including oxime O-ethers [3] or an imine.[4] During their extensive investigations of thermal reactions of tertiary amine N-oxides and nitrones Cope *et al.* did not report any elimination from nitrones. Thus, prior to the preliminary form of this work [5] no detailed report on the elimination reaction of nitrones was available.

Two literature reports, however, were of particular relevance to the problem of thermal elimination in nitrones. Emmons [6] found that the gas-phase pyrolysis of 3-phenyl-2-t-butyloxaziridine gave a mixture of nitrone, oxime, and isobutene gas and proposed that the latter two products could result from an elimination reaction of the intermediate nitrone. Kim and Weintraub postulated [7] that unstable nitrones were being

formed *in situ* in the reactions of several aldehydes with N-alkylhydroxylamines and that the putative nitrones were spontaneously breaking down to oximes and olefins at ambient temperature.

Our interest in the thermal elimination of nitrones arose from the observation that N-(fluoren-9-ylidene)-methylamine, on oxidation with m-chloroperbenzoic acid (MCPBA) (5 min; 60 °C; CHCl$_3$) gave the nitrone (1) in high yield (>85%) with traces of oxaziridine. This result was unexpected since N-alkylimines derived from benzophenone yield oxaziridines only after acid oxidation by peroxy-acid.[8]

In view of the availability of a general synthetic method for hindered diarylmethyleneamines [9,10] and the requirement for a route to hindered nitrones, a range of N-(fluoren-9-ylidene)alkylamines were obtained and oxidized with MCPBA in chloroform at 60 °C. N-(Fluoren-9-ylidene)-t-butylamine N-oxide initially proved difficult to obtain in pure form. When any significant amount of heat was used during oxidation or work-up some oxime was isolated. Even in [2H]chloro-

[1] A. C. Cope, *Org. Reactions*, 1960, **11**, 317.

[2] J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.

[3] A. C. Cope and A. C. Haven, *J. Amer. Chem. Soc.*, 1950, **72**, 4896.

[4] J. B. Bapat and D. St. C. Black, *Austral. J. Chem.*, 1968, **21**, 2521.

[5] D. R. Boyd, *Tetrahedron Letters*, 1973, 3467.
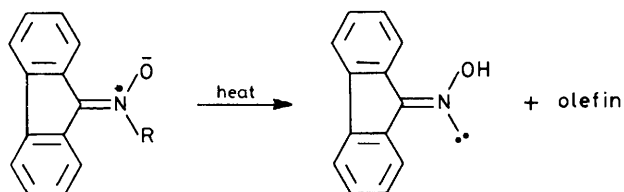
[6] W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.

[7] H. K. Kim and P. M. Weintraub, *J. Org. Chem.*, 1970, **35**, 4282.

[8] J. Bjørgo and D. R. Boyd, *J.C.S. Perkin II*, 1973, 1575.

[9] J. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, 1967, **32**, 3246.

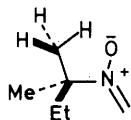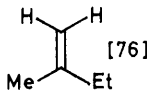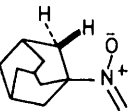[10] I. Moretti and G. Torre, *Synthesis*, 1970, 141.

TABLE 1

heat → + olefin

Nitrone	Olefin [%] [a]	Temp. (°C) [b]	Relative rates [c]	No. of β-hydrogen atoms	Relative [d] rates
(1) Me—N⁺(O⁻)=CH₂				0	
(2)		210	1 [e]	3	0.33
(3a)	[10]	180	2.4	1	2.4
(3b)	[32]	180	7.7	1	7.7
(3c)	[58]	180	14	3	4.6
(4)		180	65	6	10.9
(5)		155	1 324	3	441
(6)		80	1 600 000	9	180 000
(7a)	[24]	80	800 000	2	400 000

TABLE 1 (*Continued overleaf*)

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Nitrone	Olefin [%] [a]	Temp. (°C) [b]	Relative rates [c]	No. of β-hydrogen atoms	Relative [d] rates
(7b)	[76]	80	3 200 000	6	540 000
(8)				6	

[a] Determined by g.l.c. in the presence of other isomeric olefins. [b] Temperature at which the olefin was first evolved at a significant rate. [c] At 60 °C. [d] Corrected for the number of β-hydrogen atoms. [e] $3.4 \pm 0.04 \times 10^{-11}$ s⁻¹.

form solution at 35 °C this nitrone showed evidence of decomposition. From a sample heated at 80 °C in a vacuum line, isobutene gas and fluorenone oxime were isolated in quantitative yield.

The similarity between the Cope elimination of tertiary amine oxides and this ready nitrone elimination process was evident and prompted a more detailed study of the thermal reactions of the nitrones derived from fluorenone. Crystalline nitrone samples were heated in a vacuum system connected to a g.l.c. sampling port. The gases evolved were identified by comparison (retention times and mass spectra) with authentic samples.

The nitrones (2)—(8) all possess β-hydrogen atoms; this appears to be a requirement for thermal elimination reactions of both tertiary amine oxides and nitrones. The temperature at which elimination first occurs (Table 1) provides only a crude indication of the relative rates of elimination. Rate constants for thermal elimination were obtained by n.m.r. studies of the reaction as it occurred in a thermostatically controlled bath. Nitrones were dissolved in diphenyl ether and the progress of the reaction was followed by observing the disappearance of the *N*-alkyl signal relative to an internal standard (hexamethylbenzene). The relative rate constants at 60 °C obtained by extrapolation are shown in Table 1.

Further mechanistic information can be obtained from the composition of the olefinic products. Whereas the nitrones (2) and (4)—(6) each yield a single olefin on heating, the nitrones (3) and (7) may produce isomeric olefins. The relative rates of thermal elimination and olefin compositions shown in Table 1 may be rationalized in the following way.

(i) *Statistical factor.* The thermal elimination of nitrones (Table 1) is faster for *N*-alkyl groups bearing the optimal number of β-hydrogen atoms. This trend is analogous to that found in the Cope elimination. Cope *et al.*[1] found that when a statistical correction for the number of β-hydrogen atoms was made the relative rates of thermal elimination of tertiary amine oxides (devoid of an α-aryl substituent) were similar.

The present results show that although a similar statistical factor (entropy effect) is operative, in general this is a minor influence. Table 1 shows the relative rates for thermal elimination of the nitrones (2)—(7) after

correction for the number of β-hydrogen atoms. The rate difference between, for example, the nitrones (2) and (7) after correction is still large.

Where isomeric olefin products are obtained [(3) and (7)] the number of β-hydrogen atoms is more important. Thus the corrected relative rates of elimination of (7a and b) (or 3a—c) are similar.

(ii) *Steric factors.* The relatively fast elimination from nitrone conformation (3b) [to give (*E*)-but-2-ene] as compared with (3a) [to give (*Z*)-but-2-ene] can be most easily rationalized in terms of steric interactions favouring comformation (3b).

Dreiding and space-filling models of the nitrones (6) and (7) suggest that interlocking non-bonded interactions between the t-alkyl group and the proximate fluorenyl hydrogen atoms should be appreciable. These steric effects might be reflected in an increase in the C=N bond length, a decrease in the ⁻O···H interatomic distance and a decreased rate of rotation around the N–Cα bond.


(6) R = Me
(7) R = Et
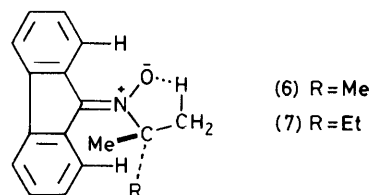
The relief of steric strain on elimination of the *N*-t-alkyl nitrones (6) and (7) would be greater than for *N*-s-alkyl [(3)—(5)] or *N*-(primary alkyl) nitrones (2) and these nitrones should show a correspondingly higher rate.

The increase in the corrected rate of elimination of (7b) over that of (6) would be consistent with increased relief of steric compression in the former. The reverse trend for the nitrones (3c) and (4) may be explained by a diminished preference by the latter nitrones for a ground-state conformation identical with that required for elimination in the transition state. The nitrones (6) and (7), however, probably have similar conformations in ground and transition states.

A low temperature [−100 °C; (CD₃)₂CO] n.m.r. analysis of the nitrone (6) did not show non-equivalent methyl groups, which could have resulted from slow rotation around the N–Cα bond.
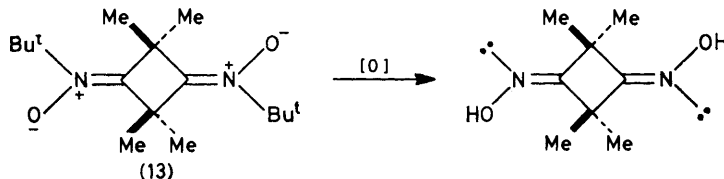
The nitrone (8), while having six β-hydrogen atoms, does not undergo thermal elimination at the temperatures studied (up to 200 °C). Similarly it has been reported [4] that the nitrone (9) did not undergo elimination at 230 °C.

The inability of the nitrones (8) and (9) to form the planar five-membered cyclic transition state necessary for N-oxide thermal elimination may again be classified as a steric factor since conformational restriction results from the ring systems present in each case.
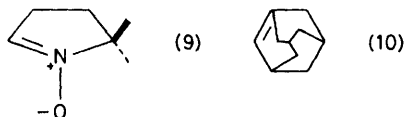
(iii) *Olefin stabilization.* The failure of the nitrone (8) to undergo thermal elimination may also or alternatively be due to the large energetic requirement for the formation of the anti-Bredt olefin adamantene (10). This highly strained olefin has previously been detected by trapping experiments at moderate temperatures.[11]

(iv) *Charge development in the transition state.* The

the effect of carbon substitution on several other representative N-t-butyl nitrones was studied. Thus, N-(4-nitrobenzylidene)-t-butylamine N-oxide (11) and its α-methyl derivative (12) also underwent thermal elimination, at 150 and 120 °C, respectively, to yield the corresponding oximes and isobutene.

Mono- and di-C-alkyl nitrones are often unstable and

$$4-O_2N \cdot C_6H_4 \cdot CR = N^+(O^-) Bu^t \quad \text{(11) } R = H$$
$$\text{(12) } R = Me$$
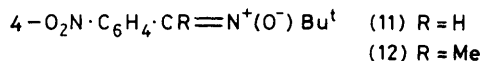
easily hydrolysed.[2] N-t-Butyl di-C-alkyl nitrones have not, to our knowledge, been reported. However, during unrelated studies [12] on the synthesis and oxidation of di-imines the di-C-alkyl nitrone (13) was isolated. The *trans*-bisnitrone (13) melted at 106 °C and eliminated isobutene at 120 °C, leaving crystals of the dioxime, m.p. 280—281° (lit.,[13] 281). This result confirms that the thermal elimination reaction of nitrones $R^1R^2C:N^+(O^-)R^3$ can occur in the systems R^1 = aryl, R^2 = H; R^1 and R^2 both alkyl; and R^1 = alkyl, R^2 = aryl.

The synthesis, separation, and stereochemistry of E-

SCHEME

contribution of olefin resonance stabilization to the relatively high rate of elimination of styrene from the nitrone (5) is difficult to estimate in view of the significant role which other factors including charge development in the transition state may play. The rates in Table 1 may be classified into three groups (primary, secondary, and tertiary N-alkyl nitrones). The unique behaviour of the nitrone (5) and the wide range of rates amongst the three categories of nitrone may be mainly due to a variation in the degree of charge separation in the transition state. It is, however, difficult at this stage to speculate further on the importance of the latter factor without having available a suitable range of nitrones containing both electron-donating and -withdrawing groups. A new range of nitrones of this type has been synthesised in these laboratories and kinetic data from thermal elimination and conclusions will be reported in Part 2 of the present series.

We emphasise that although the factors (i)—(iv) may be among the more important which lead to the wide range of rates shown in Table 1, it is difficult to provide an accurate estimate of the relative contributions from each at this stage without more accurate kinetic data.

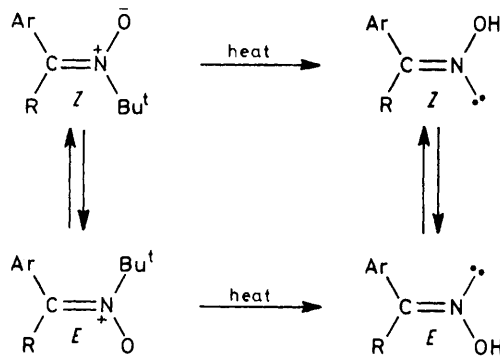Having established the general applicability of the thermal elimination process to a range of N-alkyl nitrones,

and Z-nitrones has recently been examined.[14,15] When unsymmetrically substituted nitrones are heated, E–Z isomerization may occur in both the reactants and the product oximes. Thus in the sequence shown in the

Scheme the barriers to E–Z isomerization of N-t-butyl nitrones and oximes will be <29 kcal mol⁻¹ [12] and >22—27 kcal mol⁻¹,[16] respectively (in the absence of catalysts).

Kim and Weintraub [7] examined the stereochemistry of oxime products and attempted to correlate this with the predicted stereochemistry of the transient nitrone intermediate. Since none of the aldehydes used [7] contained

[11] D. Grant, M. A. McKervey, J. J. Rooney, N. G. Samman, and G. Step, *J.C.S. Chem. Comm.*, 1972, 1186.

[12] D. R. Boyd and W. B. Jennings, unpublished data.

[13] J. L. E. Erickron and G. C. Kitchens, *J. Amer. Chem. Soc.*, 1946, **68**, 492.

[14] T. S. Dobashi, M. H. Goodrow, and E. J. Grubbs, *J. Org. Chem.*, 1973, **38**, 4440.

[15] J. Bjørgo, D. R. Boyd, D. C. Neill, and W. B. Jennings, *J.C.S. Perkin I*, 1977, 254.

[16] R. J. W. Le Fèvre and J. Northcott, *J. Chem. Soc.*, 1949, 2235.

two ortho-substituents (which under identical experimental conditions would give both and E- and Z-nitrone isomers [15]) the elusive nitrone intermediate would probably have had a Z-configuration. Since this elimination reaction of Z-nitrone intermediate occurs at 0 °C it is unlikely that the product oxime would have equilibrated. Thus Z-nitrone should yield a Z-oxime if the mechanism is analogous to that established for the

appeared,[18] and two other groups [19,20] have also reported the thermal elimination reaction of nitrones. The latter reports, taken in conjunction with the present data, demonstrate that the thermal elimination of nitrones is a general reaction which parallels the Cope elimination reaction in type but which may be of greater synthetic value in view of the more rapid elimination of suitably substituted nitrones. The large range of

TABLE 2

Imine R	M.p. (b.p.) (°C)	Found (%)			Formula	Required (%)			δ_R (CDCl$_3$)
		C	H	N		C	H	N	
Me	(125; 0.01 mmHg)	86.6	5.5	7.2	$C_{14}H_{11}N$	87.0	5.7	7.2	3.90
Et	(152; 0.02 mmHg)	87.2	6.5	6.7	$C_{15}H_{13}N$	86.9	6.3	6.8	1.50,[a,b] 4.15 [c,d]
EtMeCH	(150; 0.02 mmHg)	86.5	7.3	5.9	$C_{17}H_{17}N$	86.8	7.3	5.9	1.38,[a,f] 4.5,[e,h] 0.97,[a,b] 1.73 [c,d]
Pr^i	(125; 0.01 mmHg)	86.8	7.0	6.1	$C_{16}H_{15}N$	86.8	6.8	6.3	1.41,[a,f] 4.81 [e,g]
PhMeCH	(165; 0.01 mmHg)	89.2	6.0	5.0	$C_{21}H_{17}N$	89.0	5.9	4.9	1.70,[a,f] 5.73 [e,d]
Bu^t	(145; 0.005 mmHg)	86.9	7.5	5.7	$C_{17}H_{17}N$	86.8	7.3	5.9	1.65 [a]
EtMe$_2$C	(130; 0.03 mmHg)	86.85	7.45	5.2	$C_{18}H_{19}N$	86.7	7.7	5.6	1.40,[a] 1.06,[a,b] 1.79 [c,d]
1-Adamantyl	207	87.9	7.5	4.2	$C_{23}H_{23}N$	88.1	7.4	4.5	1.8—2.3 [h]
Nitrone R									
Me	145 (lit.,[15] 145—146)								4.28
Et	85—87 (lit.,[15] 87—88)								1.60,[a,b] 4.43 [c,d]
EtMeCH	68—70	81.1	6.9	5.6	$C_{17}H_{17}NO$	81.2	6.8	5.6	1.59,[a,f] 5.08,[e,h] 0.96,[a,b] 2.03 [e,d]
Pr^i	110 (lit.,[15] 106—107)								1.59,[a,f] 5.23 [e,g]
PhMeCH	142	84.3	5.8	4.9	$C_{21}H_{17}NO$	84.3	5.7	4.7	1.88,[a,f] 6.22 [e,d]
Bu^t	80	81.3	6.9	5.6	$C_{17}H_{17}NO$	81.2	6.8	5.6	1.85 [a]
EtMe$_2$C	67—69	81.6	7.1	5.4	$C_{18}H_{19}NO$	81.5	7.2	5.3	1.79,[a] 1.04,[a,b] 2.34 [c,d]
1-Adamantyl	155—157	83.7	7.0	4.0	$C_{23}H_{23}NO$	83.9	7.0	4.2	1.8—2.6 [h]

[a] CH$_3$. [b] Triplet. [c] CH$_2$. [d] Quartet. [e] CH. [f] Doublet. [g] Septet. [h] Multiplet.

Cope elimination. The observed [7] stereochemistry was consistent with this proposal.

When the Z-nitrone (11) was heated the thermodynamically more stable E-oxime was formed exclusively. Similarly the E-nitrone (12) gave E-oxime on heating, showing again that the reaction was thermodynamically controlled. The relatively high temperatures (120—150 °C) required for thermal elimination of the nitrones (11) and (12) thus appeared to be sufficient for equilibration of the oxime products. The thermal isomerization of E- and Z-ketone oximes in the neat form has been observed previously to be fast at 175 °C.[17]

The trans-bisnitrone (13) gave a dioxime product which appeared to be a single isomer and which is assumed to have the trans-stereochemistry from the n.m.r. spectrum [δ 2.09 (12 H, s) and 5.15 (2 H, s)].

Since the preliminary publication [5] of the present work an alternative route to the nitrones (1), (2), and (4) has

rates for thermal elimination of the nitrones (2)—(7), however, contrasts with the data from the Cope elimination.

EXPERIMENTAL

The parent imines of the nitrones (1)—(8) were prepared by condensation of fluorenone with alkylamine in the presence of titanium chloride according to previously reported methods.[9,10] The nitrones (1)—(8) were prepared by the oxidation method previously reported for oxaziridines.[21] Physical properties and microanalytical and n.m.r. data for the nitrones (1)—(8) and the parent imines are given in Table 2. Physical data of the nitrones (11) and (12) and the corresponding oximes were identical with those reported.[15,22]

Nitrones in the crystalline state were heated in a vacuum line connected to a g.l.c. sampling port. Analysis was carried out by using a 25% acetonylacetone column at ice-bath temperature. The gaseous products were identified by comparison of retention times and mass spectra with those

[17] E. G. Vassian and R. K. Murmann, J. Org. Chem., 1962, 27, 4309.
[18] R. N. Pratt, D. P. Stokes, and G. A. Taylor, J.C.S. Perkin I, 1975, 498.
[19] M. H. Goodrow, J. A. Villareal, and E. J. Grubbs, J. Org. Chem., 1974, 39, 3447.

[20] W. M. Leyshon and D. A. Wilson, J.C.S. Perkin I, 1975, 1920.
[21] D. R. Boyd, D. C. Neill, C. G. Watson, and W. B. Jennings, J.C.S. Perkin II, 1975, 1813.
[22] I. Perjhoric-Tadic, M. Hranisavljevic-Jakouljevic, S. Nesic, C. Paseual, and W. Simon, Helv. Chim. Acta, 1965, 48, 1157.

of authentic samples. Mass spectra were obtained by using an A.E.I. MS902 instrument or an A.E.I. MS30–Pye-Unicam 104 g.l.c.–mass spectrometer operating at 70 eV.

N.m.r. spectra were recorded at 60 MHz with a Varian A-60 instrument. The first-order kinetics for thermal elimination were studied by the n.m.r. technique with the nitrone (0.001M) in purified diphenyl ether (4.5 ml) containing hexamethylbenzene (0.05 g) as internal standard. Samples (0.75 ml) were pipetted into each of six n.m.r. tubes which were then heated in a thermostatically controlled (± 0.1 °C) oil-bath. Tubes were withdrawn at suitable intervals and cooled in ice, and spectra were recorded with

multiple integration of the nitrone and standard peaks. A log plot against time gave the rate constant. Extrapolation of the rate data obtained at several temperatures allowed the relative rates at 60 °C to be determined.