Oxidation of *N*-Alkylhydroxamic Acids: Interception of *N*-Acyl Nitrones

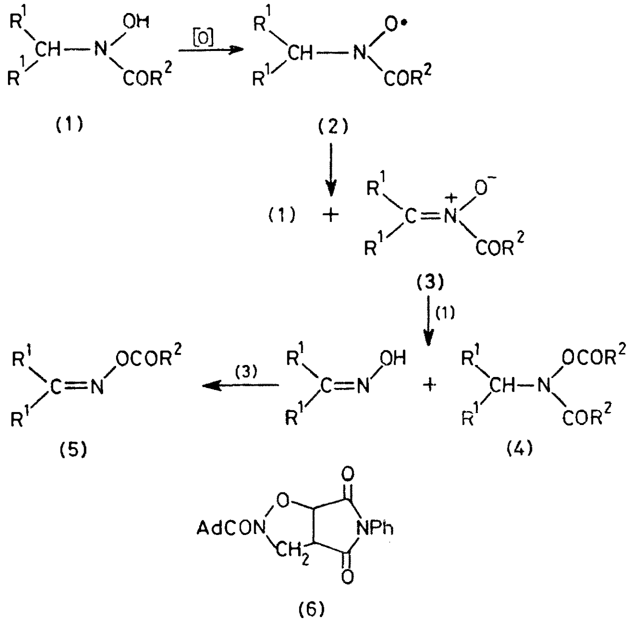
By S. Altaf Hussain, Ashutosh H. Sharma, and M. John Perkins*
(*Department of Chemistry, Chelsea College, Manresa Road, London* SW3 6LX)
and David Griller
(*Division of Chemistry, National Research Council, Ottawa, Ontario, Canada*)

Summary The acyl alkyl nitroxides (**2**), formed by one-electron oxidation of *N*-alkylhydroxamic acids, may disproportionate to give the *N*-acyl nitrones (**3**); as well as being powerful acylating agents, these transient species can be intercepted by cycloaddition to *N*-phenylmaleimide, and by 'spin-trapping' various radicals, including their nitroxide precursors.

Oxidation at nitrogen is known to be a major process in the metabolism of nitrogen-containing compounds.[1] Furthermore, the derived *N*-hydroxy-compounds have a wide range of biological activity.[2] A proper understanding of these phenomena must depend on an understanding of the chemistry of hydroxylamine derivatives. In this connection we outline here new results which substantiate Exner's conclusion[3] that transient *N*-acyl nitrones (**3**) may be formed in the one-electron oxidation of *N*-alkylhydroxamic acids (**1**), and may behave as electrophilic acylating agents.

Oxidation of *N*-isopropylbenzohydroxamic acid (**1a**) in benzene using Ag_2O–$MgSO_4$ is relatively slow. The nitroxide (**2a**) is formed (a_N 7·28, a_H 2·55 G), and the eventual reaction products include the *O*-benzoyl-derivative (**4a**) and the oxime (**5a**) (*ca.* 80 and 30% respectively, based on 0·5 mol/mol = 100%). Exner, on isolating similar products from oxidations of *N*-alkylhydroxamic acids,[3] attributed the formation of (**4**) to acylation of the unchanged hydroxamic acid by the hypothetical nitrone (**3**), and suggested that rearrangement of (**3**) gives (**5**).

When the oxidation of (**1a**) was repeated in the presence of benzylamine (1 equiv.), *N*-benzylbenzamide was produced (62%).† Evidence for the formation of an acylating agent was also obtained when the hydroxamic acid (**1a**) in ether was shaken with aqueous alkaline $K_3Fe(CN)_6$; in that case benzoic acid was obtained in good yield (82%). The ethereal solution initially turned green, consistent with formation of a high concentration of the nitroxide (**2a**)[4] (confirmed by e.s.r. spectroscopy).



a; $R^1 = Me$, $R^2 = Ph$
b; $R^1 = H$, $R^2 = Ad$ (1-adamantyl)

These results, coupled with the observation of second order kinetics for decay of the radical, are consistent with disproportionation of the initially formed nitroxide (**2a**) to give the nitrone (**3a**) (the acylating agent) and the hydroxamic acid (**1a**) (which is re-oxidised).‡

If the unusual acyl nitrone species (**3**) is indeed the acylating agent, it is unnecessary to invoke its rearrangement into (**5**), since oxime would be released in the acylation step and could itself be a precursor to (**5**) in a second acylation reaction. To test this possibility, the silver oxide oxidation of (**1a**) was repeated in the presence of benzaldehyde oxime; as expected, *O*-benzoylbenzaldehyde oxime was formed. Whilst these observations show that rearrangement of (**3**) is not required to account for the formation of (**5**), they do not establish that it does not occur.

Since the mechanism suggested does not provide a unique interpretation of the results,[5] we endeavoured to intercept the acyl nitrone by cycloaddition to a dipolarophile. Although this was unsuccessful, possibly because of the very high susceptibility of (**3a**) to competing nucleophilic attack [a major product was invariably (**4a**)], the cyclo-adduct (**6**) (m.p. 188 °C) was obtained in good yield on oxidation of (**1b**) with Ag_2O–$MgSO_4$ in the presence of *N*-phenylmaleimide.§ In this case, nucleophilic attack on the acyl nitrone carbonyl group is hindered by the tertiary R^2-group, and the reactivity of the 1,3-dipole is enhanced by the removal of the methyl substituents. In the absence of *N*-phenylmaleimide, (**4b**) is obtained. The intermediate radical (**2b**) (a_N 7·41, a_H 8·04 G), which is much less persistent than (**2a**), again decays with second order kinetics, as do the related pair of radicals EtMeCHCONMeO· and EtMeCHCON(CD_3)O·, for which a kinetic isotope effect [$k(CH_3)/k(CD_3)$] of 15 ± 2 has been found (21 °C in toluene¶).

All these results accord with initial oxidation of the hydroxamic acids to acyl alkyl nitroxides which, like other alkyl nitroxides,[6] disproportionate to nitrones. In the present system, the resulting *N*-acyl nitrones are evidently potent acylating agents.

More than one type of acyl nitroxide was recently detected by e.s.r. spectroscopy during photolysis of nitrosoamides.[7] The secondary radicals were suggested to arise *via* radical addition to acyl nitrone intermediates formed by a disproportionation pathway. We have observed analogous formation of secondary nitroxides only when (**1b**) in benzene is oxidised with alkaline $K_3Fe(CN)_6$. In that case, the predominant paramagnetic species detected appears to be an acyl nitroxide (a_N 6·96 G) which exhibits a temperature-dependent proton hyperfine structure. Two hydrogens which are non-equivalent at low temperature (a_N *ca.* 1·75 and 3·9 G) become equivalent as the temperature rises above ambient. The coalescence phenomenon is consistent with a barrier ($\Delta G^\ddagger$) of *ca.* 8·0 kcal mol^{-1} to interconversion of two conformers, which is approximately the value found for the N–O rotational barrier in *O*-alkyl derivatives of hydroxamic acids.[8] We therefore interpret

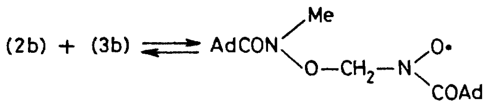
---

† Benzylamine is not benzoylated by (**3a**) under these conditions.

‡ Nitroxides could not be detected when *N*-alkylhydroxamic acids were oxidised with periodate.

§ Satisfactory analytical and spectroscopic data were obtained for all new compounds.

¶ The kinetic results were obtained by briefly irradiating a toluene solution of the appropriate *N*-alkylhydroxamic acid containing *ca.* 5% di-t-butyl peroxide, and monitoring by e.s.r. spectroscopy the decay of the radical produced, except that for (**2a**) decay of the radical produced by the $K_3Fe(CN)_6$ procedure was studied.



(7)

this spectrum in terms of the unusual nitroxide–nitrone 'spin adduct' (**7**); this is supported by the observation that its slow decay (25 °C) is accompanied by the appearance of a weaker signal due to the nitroxide (**2b**), indicative of reversible formation of (**7**). Although addition of nitroxides to nitrones has occasionally been invoked in reaction schemes,[9] direct observation of the adduct has seldom been reported.[10]

The reactions of acyl nitrones outlined here are related to those of the recently described nitrosoacyl intermediates (RCONO).[11]

We thank the S.R.C., Chelsea College, and N.A.T.O. for support, and Dr. P. F. Alewood for preliminary experiments.

(*Received*, 22*nd December* 1978; *Com.* 1372.)

---

[1] 'Biological Oxidation of Nitrogen,' ed. J. W. Gorrod, Elsevier, Amsterdam, 1978, p. 399.

[2] *E.g.* P. Mamalis in ref. 1, p. 399; L. Bauer and O. Exner, *Angew Chem. Internat. Edn.*, 1975, **13**, 376.

[3] O. Exner, *Coll. Czech. Chem. Comm.*, 1956, **21**, 1500.

[4] P. F. Alewood, S. A. Hussain, T. C. Jenkins, M. J. Perkins, A. H. Sharma, N. P. Y. Siew, and P. Ward, *J.C.S. Perkin I*, 1978, 1066, and references therein.

[5] *E.g.* T. R. Oliver and W. A. Waters, *J. Chem. Soc.* (*B*), 1971, 677.

[6] H. G. Aurich and W. Heiss, *Topics Current Chem.*, 1976, **59**, 1.

[7] E. Flesia, J.-M. Surzur, and P. Tordo, *Org. Magnetic Res.*, 1978, **11**, 123.

[8] M. Raban and D. Kost, *J. Org. Chem.*, 1972, **37**, 499.

[9] C. M. Camaggi, R. J. Holman, and M. J. Perkins, *J.C.S. Perkin II*, 1972, 501; A. Calder, A. R. Forrester, and G. McConnachie, *J.C.S. Perkin I*, 1974, 2198.

[10] The Banfield-Kenyon radical is an intramolecular adduct of this kind: R. Foster, J. Iball, and R. Nash, *Chem. Comm.*, 1968, 1414.

[11] G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1, and references therein; D. MacKay, K. N. Watson, and Lê H. Dao, *J.C.S. Chem. Comm.*, 1977, 702; C. J. B. Dobbin, D. MacKay, M. R. Penney, and Lê H. Dao, *ibid.*, p. 703; and A. R. Forrester, J. Henderson, E. M. Johansson, and R. H. Thomson, *Tetrahedron Letters*, 1978, 5139.