Acyl Nitroxides. Part I. Synthesis and Isolation

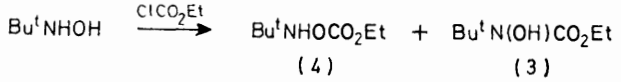
By **Paul F. Alewood, S. Altaf Hussain, Terence C. Jenkins, M. John Perkins,* Ashutosh H. Sharma, Nancy P. Y. Siew,** and **Peter Ward,** Department of Chemistry, Chelsea College, Manresa Road, London SW3 6LX

Acylation of *N*-t-butylhydroxylamine occurs predominantly on oxygen. With acetic anhydride, essentially pure *O*-acetyl-*N*-t-butylhydroxylamine is formed. This can be acylated on nitrogen, and the *O*-acetyl-group removed to give a variety of hydroxamic acids $RCON(Bu^t)OH$ which can be oxidised to isolable acyl nitroxides $RCON(Bu^t)O\cdot$ (R = alkyl, aryl, alkoxy, or dialkylamino). Other oxygen-protecting groups for *N*-t-butylhydroxylamine are discussed. The reactions have been extended to include syntheses of a number of acyl nitroxide biradicals.

Ethoxycarbonyl t-Butyl Nitroxide.—When the technique now generally referred to as spin trapping [1] was in its infancy, one system which particularly intrigued us was the scavenging, by 2-methyl-2-nitrosopropane, of polyhalogenoalkyl radicals.[2] It seemed that radicals YCX_2, where X is halogen, would normally give the 'spin adduct' (1), but that this could be readily transformed into an acyl nitroxide (2).† When Y was also halogen, halogenocarbonyl nitroxides were formed, and these readily acylated alcohols (ROH) or amines

(1) (2)

(R_2NH) to give alkoxycarbonyl (2; Y = RO) or dialkylaminocarbonyl (2; Y = R_2N) nitroxides. Both classes of radical, (1) and (2), were characterised by their e.s.r. spectra, but it was noticed that ethoxycarbonyl t-butyl nitroxide was exceptionally persistent; high concentrations of this radical accumulated, and showed little sign of decay over prolonged periods. An attempt was therefore made to isolate this radical. For this, the acylation of *N*-t-butylhydroxylamine with ethyl chloroformate was investigated.[4] When this reaction



was carried out in benzene at room temperature using two equivalents of *N*-t-butylhydroxylamine, and no other base, two products were formed in addition to t-butylhydroxylamine hydrochloride. These proved to be the desired *N*-ethoxycarbonyl derivative (3) (*ca.* 30%) admixed with the *O*-ethoxycarbonyl derivative (4) (*ca.* 70%); the latter could be removed by extraction into aqueous acid.

O-Acylation of hydroxylamines can be difficult,[5] and the result here presumably reflects a steric directing effect of the t-butyl group. A similar product distribution was obtained by carrying out the reaction with only one equivalent of *N*-t-butylhydroxylamine, but

† Although the detailed mechanism for the conversion of (1) into (2) remains obscure,[2,3] we have subsequently noticed that t-butyl trichloromethyl nitroxide can be generated by shaking a chloroform solution of 2-methyl-2-nitrosopropane with nickel peroxide. When the oxidant has settled out, the solution of radical remains substantially unchanged (e.s.r.) for a long period (hours). This is consistent with the requirement [2] for a reactive radical to remove chlorine from the trichloromethyl nitroxide as a key step in acyl nitroxide formation, which, in other systems involving t-butyl trichloromethyl nitroxide, is rapid.

[1] M. J. Perkins in Chem. Soc. Special Publ., No. 24, ed. R. O. C. Norman, London, 1970, p. 97; E. G. Janzen, *Accounts Chem. Res.*, 1971, **4**, 31; C. Lagercrantz, *J. Phys. Chem.*, 1971, **75**, 3466.

[2] C. M. Camaggi, R. J. Holman, and M. J. Perkins, *J.C.S. Perkin II*, 1972, 501.

[3] J. W. Hartgerink, J. B. F. M. Engberts, and Th. J. de Boer, *Tetrahedron Letters*, 1971, 2709.

[4] (*a*) M. J. Perkins and P. Ward, *J.C.S. Chem. Comm.*, 1973, 883; (*b*) T. C. Jenkins, M. J. Perkins, and N. P. Y. Siew, *ibid.*, 1975, 880.

[5] See *e.g.* P. A. S. Smith, 'Open-chain Nitrogen Compounds,' Benjamin, New York, 1965, vol. II, pp. 2—11; L. Bauer and O. Exner, *Angew. Chem. Internat. Edn.*, 1974, **13**, 376.

using potassium carbonate as base. However, when triethylamine was employed as base, the *O*-acyl-derivative (4) was formed in *ca.* 95% yield with only a trace of the isomeric (3). A similar result was observed with an excess of ethyl chloroformate and triethylamine, no diacylation being evident; when a benzene solution of compound (4), ethyl chloroformate, and pyridine was refluxed, (4) was recovered unchanged. On the other hand, (3), under similar conditions with pyridine, gave a good yield of the bisethoxycarbonyl derivative (5).

$$\begin{array}{c} Bu^tNOCO_2Et \\ | \\ CO_2Et \end{array}$$
(5)

These results suggest that the proportions of monoacyl derivatives result from kinetic control, and that the triethylamine-catalysed reaction may involve a more hindered acylating agent $EtO_2C\overset{+}{N}Et_3Cl^-$. The uncatalysed reaction, or that in the presence of K_2CO_3, presumably involves the chloroformate itself as acylating agent.

The *N*-hydroxycarbamate (3) in benzene was treated with nickel peroxide in the presence of sodium sulphate. This gave a deep blue solution and evaporation of solvent under reduced pressure gave the radical (2; Y = OEt) as a blue oil. The product had the e.s.r. spectrum previously attributed to this species.[2] Other spectroscopic data are recorded in the Experimental section.

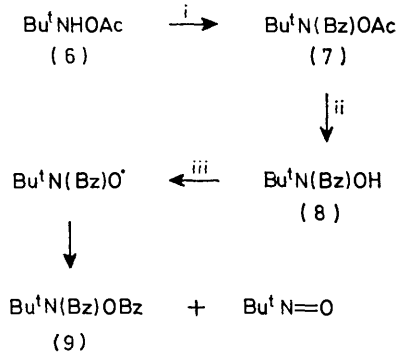
Although the radical could be obtained free of solvent, in the free state, or in concentrated solution in CCl_4 or benzene it slowly decayed to give the bisethoxycarbonyl-t-butylhydroxylamine (5) and nitrosobutane.

Methoxycarbonyl t-butyl nitroxide was obtained by a similar procedure, as a volatile blue oil.

Benzoyl t-Butyl Nitroxide.—Thus encouraged by the isolation of an acyl nitroxide, we examined the simpler case of benzoyl t-butyl nitroxide which had been characterised in solution by its e.s.r. spectrum some years earlier.[6] Direct benzoylation of two equivalents of *N*-t-butylhydroxylamine gave predominantly the *O*-benzoyl derivative together with *ca.* 15% of the desired *N*-benzoyl derivative.[7] In this case, the absence of triethylamine is apparently unimportant since in a general screening of the acylation of *N*-t-butylhydroxylamine with a variety of reagents using triethylamine as base, benzoylation gave *ca.* 23% of *N*-benzoyl derivative.[8]

It was, however, discovered that *O*-acetylation could be cleanly effected using acetic anhydride in the presence of potassium carbonate. Independently, it has recently been observed that the same result can be achieved in the absence of added base.[9] Although the carbonic acid derivative (4) had resisted acylation with ethyl chloroformate, the *O*-acetyl derivative (6) was readily benzoylated to give the diacylhydroxylamine (7). Hydrolytic removal of the acetyl group proved suprisingly difficult, but was eventually accomplished in excellent yield using barium hydroxide in ethanol. Oxidation of the resulting hydroxamic acid (8) in benzene with nickel peroxide in the presence of sodium sulphate rapidly gave a bottle-green solution, from which the benzoyl t-butyl nitroxide was obtained as a green oil, homogeneous to thin layer chromatography, but which again slowly decomposed in the absence of solvent, giving the dibenzoylhydroxylamine (9) and nitrosobutane. At 0 °C the decomposition of the neat radical had a half-life of several days; in dilute solution in benzene at room temperature this life-time is greatly prolonged.

It was subsequently found that an alternative oxidation procedure using aqueous alkaline $K_3Fe(CN)_6$ was equally satisfactory. In several cases this alternative



Reagents: i, BzCl–pyridine–benzene; ii, $Ba(OH)_2$; iii, NiO_2 or $K_3Fe(CN)_6$–OH^-

proved superior to nickel peroxide (or silver oxide) and it appears to be the general method of choice.

A number of alkanoyl and aroyl nitroxides have been obtained by the general procedure outlined here for benzoyl t-butyl nitroxide, except that some acylations of (6) with aliphatic acid chlorides employed potassium carbonate as base. Radicals prepared by these procedures are listed in Table 1. *N*-Acylation with bromoacetyl bromide gave an intermediate susceptible to nucleophilic displacement of bromine. This route to radicals of the general type $XCH_2CON(Bu^t)O\cdot$ will be described elsewhere.

The solid 4-phenylbenzoyl, 4-nitrobenzoyl, and 3,5-dinitrobenzoyl nitroxides were obtained analytically pure, and, unlike the liquid radicals, they showed little tendency to decompose in the absence of solvent. The 3,5-dinitrobenzoyl t-butyl nitroxide in particular may find some use as a selective oxidising agent.[10] The preparation of this dinitrobenzoyl nitroxide was at first complicated by a side reaction which accompanied the hydrolysis of the diacylhydroxylamine (10). Only a low yield of the desired hydroxamic acid (11) was obtained,

[6] A. L. Bluhm and J. Weinstein, *J. Amer. Chem. Soc.*, 1970, **92**, 1444; see also A. Mackor, Th. A. Wajer, and Th. J. de Boer, *Tetrahedron*, 1968, **24**, 1623.

[7] O. Exner and B. Kakac, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1656.

[8] H. G. Aurich and J. Trösken, *Chem. Ber.*, 1973, **106**, 3483.

[9] H. O. House, D. T. Manning, D. G. Melillo, L. F. Lee, O. R. Haynes, and B. E. Wilkes, *J. Org. Chem.*, 1976, **41**, 855.

[10] S. A. Hussain, T. C. Jenkins, and M. J. Perkins, *Tetrahedron Letters*, 1977, 3199.

accompanied by the cyclo-oxidation product (12). The reasonable interpretation of this result in terms of aerial oxidation of the cyclic complex (13) led to circumvention of the difficulty by carrying out the hydrolysis in the absence of oxygen. Curiously however, when the hydroxamic acid (11) was itself exposed to ethanolic barium hydroxide in the presence of air, no cyclisation occurred. The intermediacy of (11) (or its conjugate base) in the original reaction was, however, strongly indicated when it was found that brief exposure of (10) to the normal hydrolysis conditions in the presence of air also gave a good yield of (11). Only on prolonged exposure to the reaction conditions was formation of (12) observed.

TABLE 1

Acyl t-butyl nitroxides $RCON(Bu^t)O\cdot$

R	Properties *
Me	Homogeneous blue oil (t.l.c.); $\nu_{max.}(CCl_4)$ 1 710 cm^{-1}; 3% solution in CCl_4 unchanged after 7 days (dark, room temp.)
$PhCH_2$	Homogeneous blue oil (t.l.c.)
$Me(CH_2)_9$	Homogeneous blue oil (t.l.c.); $\nu_{max.}(CCl_4)$ 1 713 cm^{-1}
Ph	Homogeneous green oil (t.l.c.), solidifies on cooling below 0 °C; $\nu_{max.}(CCl_4)$ 1 687 cm^{-1}
p-$MeOC_6H_4$	Homogeneous green oil (t.l.c.); $\nu_{max.}(CCl_4)$ 1 681 cm^{-1}
p-$O_2NC_6H_4$	Green solid, m.p. 59—60 °C (from hexane) (Found: C, 55.5; H, 5.2; N, 11.6. $C_{11}H_{13}N_2O_4$ requires C, 55.7; H, 5.5; N, 11.8%), $\nu_{max.}(CCl_4)$ 1 689 cm^{-1}
3,5-$(O_2N)_2C_6H_3$	Green solid, m.p. 100 °C (from benzene) (Found: C, 46.8; H, 4.35; N, 15.2. $C_{11}H_{12}N_3O_6$ requires C, 46.8; H, 4.25; N, 14.9%), $\nu_{max.}(CCl_4)$ 1 689 cm^{-1}
p-PhC_6H_4	Green solid, m.p. 59 °C (from hexane) (Found: C, 76.2; H, 6.45. $C_{17}H_{18}NO_2$ requires C, 76.1; H, 6.8%), $\nu_{max.}(CCl_4)$ 1 673 cm^{-1}
$PhCH{=}CH$	Homogeneous yellow oil (t.l.c.); $\nu_{max.}(CCl_4)$ 1 685 and 1 627 cm^{-1}

* A detailed discussion of the spectra of these radicals will be presented elsewhere.

The structure of the cyclisation product (12) was substantiated by its rapid formation, in near quantitative yield, when the diacylhydroxylamine (14) was hydrolysed in the absence of air.

Dialkylaminocarbonyl t-Butyl Nitroxides.—Extension of the acetyl-protection procedure to the synthesis of *N*-alkoxycarbonyl-*N*-t-butylhydroxylamines, *e.g.* (3), proved generally unsatisfactory because of the difficulty of removing the acetyl group without disturbing the nitrogen substituent. Furthermore, attempts to acylate the *O*-acetyl-*N*-t-butylhydroxylamine with dimethylcarbamoyl chloride were unsuccessful. However, the acetylhydroxylamine reacted readily with phosgene to give the chlorocarbonyl derivative (15), and this condensed with secondary amines to give the *N*-acetoxyureas (16). These could be hydrolysed by the barium hydroxide procedure or cleaved by reaction with excess amine, to give the corresponding *N*-hydroxyureas, which could, in turn, be oxidised to exceedingly stable red radicals (17). It was frequently difficult to obtain good n.m.r. spectra of the *N*-hydroxyureas without adding a little hydrazobenzene to reduce traces of nitroxide, presumably formed by aerial oxidation. It will be shown in a separate paper that the OH bonds in these hydroxyureas are weaker than those in the *N*-t-butylhydroxamic acids, *e.g.* (8) (*cf.* ref. 4*b*).

$Bu^tN(COCl)OAc \xrightarrow{R_2NH} Bu^tN(CONR_2)OAc$

(15) (16)

$Bu^tN(CONR_2)O\cdot$ $Bu^tN(CO_2Ph)O\cdot$

(17) (18)

The chlorocarbonyl derivatives (15) can also be used to acylate alcohols, and, using 4-dimethylaminopyridine [11] as base, phenol. In the latter case it has been possible selectively to cleave the acetoxy-group using pyrrolidine, and the resulting *N*-phenoxycarbonyl-*N*-t-butylhydroxylamine could be oxidised to the phenoxycarbonyl nitroxide (18); this, however, proved to be one of the least stable of this series of radicals, decomposing rapidly in solution, before removal of solvent was possible.

Data on radicals obtained by these procedures are given in Table 2.

TABLE 2

Radicals prepared *via* *N*-acetoxy-*N*-t-butylcarbamoyl chloride

Radical $RCON(Bu^t)O\cdot$	Properties
R = Piperidino	Pale red prisms, m.p. 38–39 °C from hexane (Found: C, 60.1; H, 9.9; N, 14.0. $C_{10}H_{19}N_2O_2$ requires C, 60.3; H, 9.6; N, 14.1%), $\nu_{max.}(CCl_4)$ 1 691 cm^{-1}
R = Morpholino	Red-brown solid, m.p. 29 °C from hexane, $\nu_{max.}(CCl_4)$ 1 700 cm^{-1}
R = Pyrrolidinyl	Red oil, $\nu_{max.}(CCl_4)$ 1 670 cm^{-1}
R = Phenoxy	Yellow-green solution in benzene; rapidly decomposes before removal of solvent

Alternative Approaches to Oxygen Protection of N-*t-Butylhydroxylamine.*—The ease and efficiency of preparation of the *O*-acetyl-derivative (6) make this a convenient *O*-protected form of *N*-t-butylhydroxylamine. However, for a number of investigations it seemed desirable that we should find a protecting group which could be removed under milder conditions than those provided by

[11] See *e.g.* G. Hofle and W. Steglich, *Synthesis*, 1972, 619.

ethanolic barium hydroxide. Although this goal has not been fully realised, we note briefly some results which have been obtained.

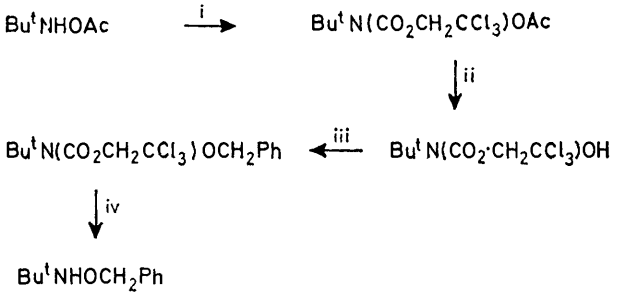
Acylation of *N*-t-butylhydroxylamine with benzyl chloroformate was not a particularly clean reaction, although the *O*-acylated derivative was isolated. However, attempts to effect benzoylation of this were also relatively unsuccessful and this approach was abandoned.

Acylation using 2,2,2-trichloroethyl chloroformate appeared more promising; the *O*-acylated derivative (19) was isolated in fair yield as a crystalline solid, but the product resisted acylation at nitrogen except with

$Bu^tNHOCO_2CH_2CCl_3$ (19) $Bu^tN(COCl)OCO_2CH_2CCl_3$ (20)

phosgene to give (20). Although compound (20) potentially affords an alternative route to alkoxycarbonyl and aminocarbonyl nitroxides, it has not yet been extensively investigated.

Since, in unpublished work, we have established that *N*-acyl-*O*-benzyl-*N*-t-butylhydroxylamines can be debenzylated by hydrogenolysis without cleavage of the N–O bond, approaches to *O*-benzyl-*N*-t-butylhydroxylamine were examined. *N*-t-Butylhydroxylamine is cleanly benzylated with benzyl chloride, but exclusively on nitrogen. Even when solutions believed to contain the anion Bu^tNHO^- were treated with benzyl chloride, the major product was again the *N*-benzyl-derivative, but admixed with a second compound (*ca.* 35%) con-



Reagents: i, $ClCO_2CH_2CCl_3$; ii, $Ba(OH)_2$; iii, $PhCH_2Br$; iv, Zn–HOAc

SCHEME 1

sidered to be the *O*-benzyl derivative. This *O*-benzyl-derivative has subsequently been synthesised by the sequence shown in Scheme 1. In this sequence, it was found that the acetyl group *could* be cleaved from the *NO*-diacyl-intermediate without disrupting the *N*-alkoxycarbonyl substituent. Although the overall procedure was surprisingly efficient, its complexity does not justify extensive experimentation with benzyl as an oxygen-protecting group.

O-Tritylation of *N*-t-butylhydroxylamine proved more straightforward, but the product could not be acylated. When, at −78 °C, it was treated with butyl-lithium followed immediately by benzoyl chloride, phenyl trityl ketone was produced, presumably by fragmentation of the intermediate anion.

[12] C. B. Reese and J. C. M. Stewart, *Tetrahedron Letters*, 1968, 4273.

Finally, we have recently investigated more base-sensitive acyl groups such as methoxyacetyl [12] for oxygen protection. This approach seems promising, and further work is in hand.

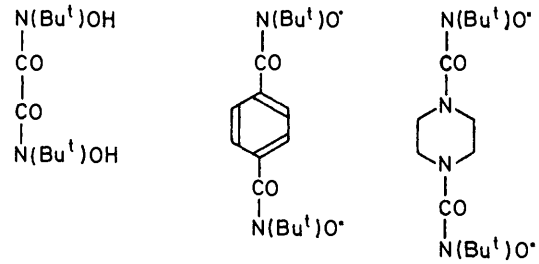
The removal of the acetyl group from *O*-acetyl-*N*-benzoyl-*N*-t-butylhydroxylamine (7) by the barium hydroxide procedure was far superior to acid-catalysed

$$Bu^tN\bar{O}CPh_3 \longrightarrow Bu^tN{:}O + {}^-CPh_3$$

hydrolysis, or hydrolysis with other base systems, although, curiously, sodium ethoxide in ethanol was perfectly satisfactory for the selective *O*-debenzoylation of (9) (see also ref. 8). The use of aroyl protecting groups for oxygen has not, however, been further explored. The solid *O*-*p*-nitrobenzoyl derivative prepared in good yield by Exner and Holubek [13] looks attractive in this respect, although removal of the *O*-acyl group from the corresponding *NO*-bis-*p*-nitrobenzoyl derivative was rather inefficient.[13]

Reductive deacetylation of (7) by prolonged treatment with sodium borohydride in basified ethanol was moderately successful (75%). There was no reaction with lithium borohydride in ether.

Biradicals.—Using the general procedures already outlined, the bishydroxamic acids listed in Table 5 have been prepared. With the exception of the *NN'*-dihydroxyoxamide (21), these have all been oxidised to biradicals. Two of the biradicals, that from terephthalic acid (22), and the bis(dialkylaminocarbonyl nitroxide) from piperazine (23), have been isolated as analytically pure solids, the other biradicals were generated only in



(21) (22) (23)

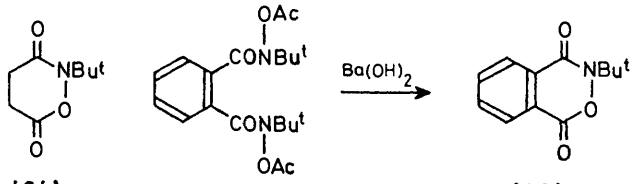
solution. Oxidation of compound (21) gave nitrosobutane in good yield ($\nu_{max.}$ 1 565 cm^{-1}) presumably by fragmentation of a paramagnetic intermediate.

In the course of related experiments, it was noted that with succinyl chloride the *O*-acetyl-*N*-t-butylhydroxylamine (6) gave the cyclic 1,2-oxazinedione (24), and, although phthaloyl chloride gave a normal reaction with (6), on attempted hydrolysis of the product an oxazinedione (25) was again obtained. Compound (25) was also prepared from phthaloyl chloride and *N*-t-butylhydroxylamine. By analogy with the photolysis of *NO*-diacyl- [14]

[13] O. Exner and J. Holubek, *Coll. Czech. Chem. Comm.*, 1965, **30**, 940.

[14] B. Danieli, P. Manitto, and G. Russo, *Chem. and Ind.*, 1969, 329; 1971, 203.

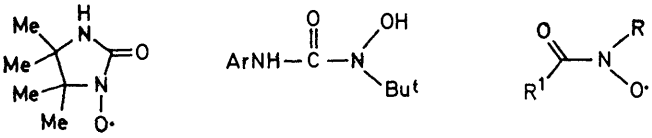
and triacyl-hydroxylamines,[15] it might be envisaged that the photolyses of (24) and (25) would give β-lactams, or products derived therefrom. Investigations of the photolysis of these and related compounds will be reported elsewhere.



(24) (25)

DISCUSSION

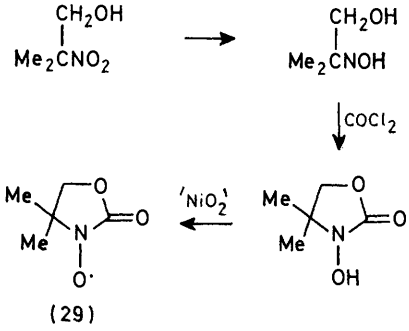
Acyl nitroxides have long been recognised by their e.s.r. spectra,* but perhaps surprisingly, until our preliminary report,[4a] it had apparently not been suggested that any of this class would be sufficiently ' persistent ' to permit their isolation. In fact, closely related iminocarbonyl nitroxides were already known from the efforts of Aurich [20] and Ullman [21] and their colleagues. Indeed, in the course of their investigations into the chemistry of cyclic imino nitroxides and the related nitronyl nitroxides, Ullman's group had generated a concentrated solution of the cyclic aminocarbonyl nitroxide (26).[21]



(26) (27) (28)

On attempted isolation, however, this rapidly decomposed. Two differences can be identified between (26) and the crystalline aminocarbonyl nitroxides obtained in the present work. These are (i) the presence of the NH group, and (ii) the necessarily *syn*-relationship between the carbonyl oxygen and the nitroxide oxygen in (26). Acyclic *N*-hydroxyureas (27) closely related to (26) are also known,[22,23] and, whilst nitroxides have not been isolated from their oxidation, the e.s.r. spectra of these nitroxides have been extensively documented.[22]

It has been argued [8,24] that the acyclic acyl nitroxides adopt an *anti*-conformation (28), and this is intuitively reasonable. To explore the point,[8,24] we extended our work on alkoxycarbonyl nitroxides to the cyclic radical (29), generated by the sequence shown in Scheme 2. Oxidation of the intermediate *N*-hydroxyoxazolinone gives a peacock blue solution, removal of the solvent from which leaves a blue oil, and although this appears as one spot on t.l.c. it fairly rapidly decomposes to a complex mixture of products. The rate of decomposition is greater than that of ethoxycarbonyl t-butyl nitroxide, but the distinction is not comparable to that in the aminocarbonyl series where, whilst (26) is too unstable to be isolated, radicals (17) are very stable indeed. This



(29)

SCHEME 2

suggests that the instability of (26) is probably to be associated with the presence of the NH-group, but this conclusion must be regarded as tentative. On dilution of (29) in benzene, and examination by e.s.r., the product showed a major paramagnetic component giving a three-line spectrum with a_N = 7.52 G. There was, however, a second radical present; this also gave a three-line spectrum, with a_N = 14.5 G, which has not been identified.

The nitrogen splitting of 7.52 found for (29) is to be compared with 8.35 G [2] for the alkoxycarbonyl nitroxide generated by oxidation of (3). This is in line with the general conclusion that cyclic acyl nitroxides have a lower a_N than related ayclic radicals where the carbonyl and nitroxide oxygens have been suggested to be *anti*.[8] The size of the ring, and associated strain, may however be important, since seven- and nine-membered ring acyl nitroxides have been generated which have a_N values slightly larger than those of appropriate acyclic models.[24] The structure of acyl nitroxides will be considered further in a future paper.†

Finally, it is interesting to reflect on the possible uses

* In addition to the acyl t-alkyl nitroxides, less persistent acyl,[16] acyl alkyl,[17] acyl aryl,[18] and diacyl [15,19] nitroxides have been characterised by their e.s.r. spectra.

† *Note added in proof:* *X*-Ray crystallographic examination of the 3,5-dinitrobenzoyl nitroxide obtained by oxidation of (11) shows the RCON(R)O· grouping to be essentially coplanar, and confirms that, in the solid at least, the oxygens are *anti*-related. S. A. Hussain, T. J. King, and M. J. Perkins, unpublished observations.

[15] F. R. Stermitz and D. W. Neiswander, *J. Amer. Chem. Soc.*, 1973, **95**, 2630.

[16] J. V. Ramsbottom and W. A. Waters, *J. Chem. Soc.* (*B*), 1966, 132.

[17] D. F. Minor, W. A. Waters, and J. V. Ramsbottom, *J. Chem. Soc.* (*B*), 1867, 180; W. C. Danen and R. W. Gellert, *J. Amer. Chem. Soc.*, 1972, **94**, 6853.

[18] H. G. Aurich and F. Baer, *Tetrahedron Letters*, 1965, 3879; A. R. Forrester, M. M. Ogilvy, and R. H. Thomson, *J. Chem. Soc.* (*C*), 1970, 1081.

[19] H. Lemaire and A. Rassat, *J. Chim. phys.*, 1964, 1580; A. Calder, A. R. Forrester, and R. H. Thomson, *J. Chem. Soc.* (*C*), 1969, 512.

[20] H. G. Aurich and K. Kabs, *Angew. Chem. Internat. Edn.*, 1970, **9**, 636.

[21] E. F. Ullman, L. Call, and J. H. Osiecki, *J. Org. Chem.*, 1970, **35**, 3623.

[22] H. G. Aurich, H. G. Scharpenberg, and K. Kabs, *Tetrahedron Letters*, 1970, 3559; D. Sarantaski, T. K. Watts, and B. Weinstein, *Tetrahedron*, 1971, **27**, 2573; V. S. Griffiths and G. Parlett, *J. Chem. Soc.* (*B*), 1969, 997; H. G. Aurich and K. Stork, *Tetrahedron Letters*, 1972, 555.

[23] G. Zinner and B. Geister, *Arch. Pharm.*, 1974, **307**, 39.

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

of the radicals documented here. The dialkylaminocarbonyl t-butyl nitroxides are probably sufficiently stable and unreactive to find some use as spin labels, but this is less likely for the alkanoyl or aroyl nitroxides which are more reactive. As has been intimated previously,[10] and will be documented fully in a subsequent paper, this reactivity can be controlled by varying the acyl group, so that a range of radical reagents with the general oxidising character of Fremy's radical,[25] but readily soluble in organic solvents, may be to hand.

EXPERIMENTAL

I.r. spectra were normally recorded on CCl_4 solutions. Proton n.m.r. spectra were recorded at 60 or 90 MHz on solutions in $CDCl_3$; δ values are quoted relative to internal tetramethylsilane. Column and thin layer chromatography was on silica gel.

N-t-Butylhydroxylamine (m.p. 64—65 °C) was prepared following the general procedure of Calder, Forrester, and Hepburn;[26] it was found that the yield of product generally fell if batches of 2-methyl-2-nitropropane in excess of 60 g were reduced, and reactions were normally carried out on this scale. The product may be purified by crystallisation from light petroleum (b.p. 60—80 °C), or by sublimation *in vacuo*.

Ethoxycarbonyl t-Butyl Nitroxide.—(a) *Acylation of t-butylhydroxylamine with ethyl chloroformate.* (i) Ethyl chloroformate (0.61 g) was added dropwise with stirring during 10 min to a solution of t-butylhydroxylamine (1.0 g) in dry benzene (15 ml). The mixture (from which hydrochloride had separated) was stirred overnight, poured into water, and the water was extracted with ether. The ether solution contained two major components (t.l.c.), the less polar of which was removed by repeated washing with dilute HCl (3M). The remaining ether solution was dried ($MgSO_4$) and evaporated to leave a pale yellow oil (0.273 g, 30%) homogeneous on t.l.c. This was identified as *ethyl* N-*hydroxy*-N-*t-butylcarbamate* (3) from the following spectroscopic data: $\nu_{max.}$ 3 600—3 100 (OH) and 1 680 (C=O) cm^{-1}; δ 1.38 (s, 9 H, Bu^t), 1.26 (t, 3 H, J = 7 Hz, CH_3), 4.22 (q, 2 H, J = 7 Hz, CH_2), and 7.0 (s, 1 H, OH); *m/e* 161 (M^+). (ii) A similar yield of the *N*-hydroxycarbamate (3) could be obtained using one equivalent of t-butylhydroxylamine and an excess of K_2CO_3. (iii) To a stirred solution of the hydroxylamine (1.0 g) and triethylamine (2.27 g) in benzene (20 ml) at 0 °C was slowly added ethyl chloroformate (1.22 g) in benzene (5 ml) during ½ h. Stirring was continued for ½ h at 0 °C, and then at room temperature for 8 h. The mixture was poured into water and ether was added. The aqueous layer was just acidified with 2M-HCl; the ether solution was removed and washed successively with water and aq. $NaHCO_3$ and then dried ($MgSO_4$). Evaporation of the ether left an oil (1.93 g, 95%) identified from the following spectroscopic data as O-*ethoxycarbonyl*-N-*t-butylhydroxylamine* (4): $\nu_{max.}$ 3 240 (NH) and 1 750 (C=O) cm^{-1}; δ 1.19 (s, 9 H, Bu^t), 1.34 (t, 3 H, J = 7 Hz, CH_3), and 4.21 (q, 2 H, J = 7 Hz, CH_2), NH not observed. This product was contaminated with a trace of the isomeric compound (3) (singlet at δ 1.36), and was identical with the acid-soluble product in (i) above. (iv) Repetition of (iii) using 2 equivalents of ethyl chloroformate and 4 equivalents of Et_3N gave only the *O*-acylated product. (v) When the product from (iii) (0.8 g), ethyl chloroformate (0.815 g), and pyridine (0.79 g) were refluxed in benzene (10 ml) for ½ h the *O*-acyl derivative (4) was recovered unchanged. (vi) When the *N*-hydroxycarbamate (3) (30 mg), ethyl chloroformate (24 μl), and pyridine (40.5 μl) were refluxed in benzene (1 ml) for ½ h, a new product was obtained, after acid washing, as a pale yellow oil which on the basis of spectral evidence [$\nu_{max.}$ 1 790 and 1 730 cm^{-1}; δ 1.30 (s, 9 H, Bu^t), 1.25 (t, 3 H, J = 7 Hz, CH_3), 1.18 (t, 3 H, J = 7 Hz, CH_3), 4.00 (q, 2 H, J = 7 Hz, CH_2), and 4.08 (q, 2 H, J = 7 Hz, CH_2); *m/e* 233 (M^+)] was concluded to be O-*bis-ethoxycarbonyl*-N-*t-butylhydroxylamine* (5).

(b) *Oxidation of the* N-*hydroxycarbamate* (3) *with nickel peroxide.* The *N*-hydroxycarbamate (3) (131 mg) in benzene (5 ml) was stirred with nickel peroxide (0.3 g) and anhydrous sodium sulphate (0.05 g) for 15 min at room temperature. The resulting deep blue solution was filtered and solvent was removed from the filtrate under reduced pressure to leave a blue oil (129 mg) which moved as a single blue spot on t.l.c. (CH_2Cl_2), $\nu_{max.}$(CCl_4) 1 747 cm^{-1}. On dilution to *ca.* 10^{-5}M, the blue product had an e.s.r. spectrum indistinguishable from that of ethoxycarbonyl t-butyl nitroxide.

(c) *Decomposition of ethoxycarbonyl t-butyl nitroxide.* The *N*-hydroxycarbamate (3) (10 mg) was dissolved in CCl_4 (0.5 ml) and treated with an excess of nickel peroxide and sodium sulphate during 15 min. The solution was filtered and solvent removed from the filtrate; CCl_4 (200 μl) was added to the solution which was then left in the dark in a sealed vessel for 15 days. After this time, examination by i.r. showed the characteristic split carbonyl of the bis-ethoxycarbonylhydroxylamine (5), and an additional peak (1 565 cm^{-1}) consistent with the formation of nitrosobutane (*ca.* 75%). In a preparative experiment, the bis-ethoxycarbonylhydroxylamine was isolated (prep. t.l.c.) in good yield (>80%, identical with the product described above).

(d) *Preparation of methyl* N-*hydroxy*-N-*t-butylcarbamate.* Methyl chloroformate (5.2 g) was added dropwise during 20 min to a well stirred mixture of K_2CO_3 (15.5 g) and t-butylhydroxylamine (5 g) in dry benzene (80 ml). The mixture was stirred for 1 h, diluted with ether (100 ml), and filtered. The filtrate was washed thoroughly with 2M-HCl (4 × 50 ml) to remove the *O*-acylation product, and then with 2M-NaOH (3 × 50 ml) to remove the *N*-acylation product from neutral bis-acylation product. The combined alkaline extracts were acidified to pH 1 (HCl) and extracted with ether (3 × 100 ml). The ether solution was dried and solvent was removed to give *methyl* N-*hydroxy*-N-*t-butylcarbamate* as a colourless oil (1.27 g, 16%), $\nu_{max.}$ 3 600—3 000 (OH) and 1 683 (C=O) cm^{-1}; δ 1.35 (s, 9 H, Bu^t), 3.68 (s, 3 H, CH_3), and 6.9br (1 H, removed by D_2O); *m/e* 147 (M^+). Oxidation of this gave methoxycarbonyl t-butyl nitroxide as a blue-mauve oil with an irritating odour; $\nu_{max.}$(CCl_4) 1 747 cm^{-1}; $\lambda_{max.}$(ε) 225 (3 920), 245sh (2 955), 601 (2.8), 640sh (2.5), and 690sh (1.6).

Benzoyl t-Butyl Nitroxide.—(a) *Acetylation of* N-*t-butylhydroxylamine with acetic anhydride.* To a stirred solution of *N*-t-butylhydroxylamine (5.0 g, 56.2 mmol) in dry ether (60 ml) containing powdered anhydrous potassium carbonate (15.5 g) was added, dropwise, acetic anhydride (5.43 g, 53 mmol). When the reaction had subsided (1 h), the inorganic solids were removed and washed with ether, and

[25] H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, 1971, **71**, 229.

[26] A. Calder, A. R. Forrester, and S. P. Hepburn, *Org. Synth.*, 1972, **52**, 78.

the combined ether solution and washings were dried (Na_2SO_4) and evaporated to give *O*-acetyl-*N*-t-butylhydroxylamine (6) as a colourless, volatile, sweet smelling liquid (7.22 g, 98%). This product contained only a trace of *N*-acetyl derivative, and was used in subsequent reactions without further purification, although it may be distilled.

(b) *Preparation of* O-*acetyl*-N-*benzoyl*-N-*t-butylhydroxylamine.* To a stirred solution of *O*-acetyl-*N*-t-butylhydroxylamine (11.8 g, 89.6 mmol) in dry benzene (100 ml) was added dry pyridine (7.9 g, 100 mmol) and benzoyl chloride (12.3 g, 87.2 mmol). The mixture was boiled under reflux for 1½ h after which it was cooled and extracted with 2M-HCl (3 × 100 ml) and 2M-NaOH (2 × 100 ml); finally it was washed with water (3 × 100 ml). The benzene solution was then dried (Na_2SO_4), and solvent was removed to leave a yellow oil which solidified. One crystallisation from hexane–CH_2Cl_2 (5 : 1) gave O-*acetyl*-N-*benzoyl*-N-*t-butylhydroxylamine* (7), m.p. 61.0—61.5 °C (14.7 g, 72%) (Found: C, 66.3; H, 7.4; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%), $\nu_{max.}$ 1 804 and 1 661 cm^{-1}; δ 1.52 (s, 9 H, Bu^t), 1.76 (s, 3 H, CH_3), and 7.1—7.8 (m, 5 H, Ph).

(c) *Hydrolysis of* O-*acetyl*-N-*benzoyl*-N-*t-butylhydroxylamine.* Hydrated barium hydroxide (38 g) was added to a solution of the above diacylhydroxylamine (6.0 g) in ethanol (120 ml) and the mixture was shaken for 40 min. After this the solvent was evaporated, ethanol (50 ml) added, and the mixture shaken for a further 30 min. This was repeated to ensure complete hydrolysis. The solvent was again removed and water (60 ml) was added followed by sufficient 12M-HCl as to acidify the mixture to pH 1. The resulting mixture was extracted with ether (3 × 100 ml) and the combined extracts were washed with aqueous sodium hydrogen carbonate and water, and then dried (Na_2SO_4). Removal of solvent gave an oil which solidified. One crystallisation from hexane–CH_2Cl_2 (5 : 1) gave the required *N*-t-butylbenzohydroxamic acid (8), m.p. 113—114 °C (lit. 109 °C,[8] 113 °C [7]), in essentially quantitative yield (4.8 g, 97%). This had $\nu_{max.}$ 3 600—2 700 (OH) and 1 605 (C=O) cm^{-1}; δ 1.32 (s, 9 H, Bu^t), 7.29 (s, 5 H, Ph), and 8.45br (s, 1 H, OH, removed by D_2O).

(d) *Oxidation of* N-*t-butylbenzohydroxamic acid to benzoyl t-butyl nitroxide.* (i) A solution of the hydroxamic acid (1.50 g) in CH_2Cl_2 (150 ml) was shaken with an excess of a saturated solution of potassium ferricyanide in 2M-NaOH (100 ml). The CH_2Cl_2 solution immediately became dark green, and after 1 min this was separated, washed with water (3 × 40 ml), and dried (Na_2SO_4). Removal of the solvent at room temperature afforded the nitroxide as a green oil (1.48 g, 99%) homogeneous to t.l.c. The radical had $\nu_{max.}$ 1 687 (CCl_4), and on dilution to *ca.* 10^{-5}M in benzene gave the three-line e.s.r. spectra of benzoyl t-butyl nitroxide. This procedure has proved quite general, and other suitable solvents include benzene, CCl_4, and ether (although there is a slow reaction with ether).

(ii) Oxidation can alternatively be effected by nickel peroxide or silver oxide, preferably in the presence of a drying agent, *e.g.* in benzene, but the reaction is relatively slow, does not always go to completion, and with some hydroxamic acids it appears to give soluble metal complexes.

TABLE 3

Intermediates in the synthesis of aroyl t-butyl nitroxides

	ArCON(Bu^t)OAc				ArCON(Bu^t)OH			
	M.p. (°C)	% Found (Calc.)			M.p. (°C)	% Found (Calc.)		
Ar	[% yield]	C	H	N	[% yield]	C	H	N
p-$MeOC_6H_4$	Oil (not purified)				113—114	64.6	7.6	6.4
					[56]	(64.6	7.7	6.3)
p-$O_2NC_6H_4$	112—113	55.5	5.6	10.0	142—143 *	55.7	6.0	12.0
	[77]	(55.7	5.8	10.0)	[87]	(55.5	5.9	11.8)
p-PhC_6H_4					137—138	‡ 76.4	7.0	4.9
						(75.8	7.1	5.2)
3,4,5-$I_3C_6H_2$	[Not purified]				191	22.85	2.3	2.2
						(23.1	2.1	2.45)
3,5-$(O_2N)_2C_6H_3$	106—108	48.2	4.5	13.1	160 §	46.8	4.8	14.95
	[74]	(48.0	4.65	12.9)	[90]	(46.6	4.6	14.8)
PhCH=CH	Oil [not purified]				93—93.5	71.2	8.2	6.5
					[63] †	(71.2	7.8	6.4)

* Lit.[13] m.p. 142 °C. † Based on *O*-acetyl-*N*-t-butylhydroxylamine. ‡ Prepared in 20% yield by direct acylation of t-butylhydroxylamine, along with O-p-*phenylbenzoyl*-N-*t-butylhydroxylamine* (51%), m.p. 64—65°. § Hydrolysis of acetyl compound under N_2, see below.

Details of the study of the decomposition of benzoyl t-butyl nitroxide will be given in a subsequent paper.

Other Aroyl t-Butyl Nitroxides.—Essentially the same procedure as that described above was adopted for the synthesis of several other aroyl t-butyl nitroxides, as well as cinnamoyl t-butyl nitroxide. The results are summarised in Table 3.

The *N*-aroylhydroxylamines (hydroxamic acids) listed in Table 3 were all oxidised by the ferricyanide procedure described above to the corresponding acyl nitroxides, some data for which are listed in Table 1.

Preparation of *N*-(3,5-dinitrobenzoyl)-*N*-t-butylhydroxylamine (11) by hydrolysis of the *O*-acetyl derivative (10) by the normal procedure, was unsatisfactory, with a yield of *ca.* 30%, although when the reaction time was reduced to 15 min this rose to nearly 90%. Further repetition of the hydrolysis, with the reaction time extended to 2 h, gave a new, neutral product, m.p. 138—139 °C from ethanol. This had carbonyl absorption at $\nu_{max.}$ 1 700 cm^{-1} (Nujol), and a very simple n.m.r. spectrum: δ 1.69 (s, 9 H, Bu^t), 8.8, and 9.1 (both d, 1 H, J = 3 Hz, aromatic). From this it was concluded that the product was probably 5,7-*dinitro*-2-*t-butylbenzisoxazol*-3-*one* (12) (Found: C, 46.8; H, 3.7; N, 15.0. $C_{11}H_{11}N_3O_6$ requires C, 47.0; H, 3.9; N, 14.9%).

Prolonged hydrolysis of the *O*-acetyl compound under N_2 gave the hydroxamic acid in 90% yield. When the hydroxamic acid (crystallised from ethanol) (500 mg) was itself shaken with $Ba(OH)_2 \cdot 8H_2O$ (3.2 g) in ethanol (20 ml) for 1½ h, and the solution then acidified, it was recovered essentially quantitatively, irrespective of whether or not the base treatment was carried out in the presence of air.

Alternative Synthesis of the Benzisoxazolone.—*O*-Acetyl-*N*-t-butylhydroxylamine was acylated in the normal way, using 2-chloro-3,5-dinitrobenzoyl chloride, to give O-*acetyl*-N-(2-*chloro*-3,5-*dinitrobenzoyl*)-N-t-*butylhydroxylamine* (14), m.p. 142 °C (from hexane–CH_2Cl_2). This had $\nu_{max.}$ 1 678 and 1 810 cm^{-1} (Nujol); δ 1.55 (s, 9 H, Bu^t), 1.86 (s, 3 H, CH_3), and 8.32 and 8.68 (both d, 1 H, J = 3 Hz) (Found: C, 43.5; H, 4.0; N, 11.8. $C_{13}H_{14}ClN_3O_7$ requires C, 43.3; H, 3.9; N, 11.7%). This compound was then exposed to the normal hydrolysis conditions for 1 h under N_2. Examination of the organic products by n.m.r. spectroscopy showed them to consist of approximately equal proportions of the unchanged *O*-acetyl compound and the benzisoxazolone reported above. Similar hydrolysis under N_2 for 3 h gave the benzisoxazolone in *ca.* 90% yield, identical with the above product (m.p., mixed m.p., and n.m.r. spectrum).

Alkanoyl t-Butyl Nitroxides.—The precursors to aliphatic acyl t-butyl nitroxides were prepared according to the general procedure described for benzoyl t-butyl nitroxide, except that in some instances the acylation of *O*-acetyl-*N*-t-butylhydroxylamine was effected using an excess of K_2CO_3 in place of the organic base. The results are summarised in Table 4.

The *N*-alkanoylhydroxylamines (hydroxamic acids) listed in Table 4 were all oxidised by the ferricyanide procedure described above to the corresponding acyl nitroxides, some data for which are listed in Table 1.

Preparation of O-*acetyl*-N-*chlorocarbonyl*-N-*t-butylhydroxylamine* (N-*acetoxy*-N-*t-butylcarbamoyl chloride*). A solution of *O*-acetyl-*N*-t-butylhydroxylamine (10 g) in ether (25 ml) was added during 5 min to a solution of phosgene (*ca.* 30 g) in benzene (250 ml) under N_2, and the mixture was stirred for 3 h after which the precipitate which formed had almost entirely disappeared. Nitrogen was then bubbled through the stirred solution overnight to remove excess of phosgene and most of the solvent. The remaining solvent was removed under reduced pressure, leaving crude N-*acetoxy*-N-*t-butylcarbamoyl chloride* (15) as a pale yellow oil (12.5 g, 85%), which exhibited $\nu_{max.}$ 1 810 and 1 740 cm^{-1} and δ(CCl_4) 1.43 (s, 9 H, Bu^t), 2.19 (s, 3 H, CH_3). This was normally used without further purification, but could be purified by distillation, b.p. 86—88 °C at 24 mmHg (Found: C, 43.6; H, 6.5; N, 7.4. $C_7H_{12}ClNO_3$ requires C, 43.4; H, 6.3; N, 7.2%).

O-*Acetyl*-N-*piperidinocarbonyl*-N-*t-butylhydroxylamine* (N-*acetoxy*-N-*t-butyl*-N′N′-*pentamethyleneurea*).—To a stirred solution of the above carbamoyl chloride (4.0 g) in dry benzene (25 ml) was added dry pyridine (2.4 g), followed by dry piperidine (5.0 g) in benzene (5 ml). The mixture was stirred at room temperature for 8 h, ether (50 ml) was added, and the mixture was washed with 2M-HCl (2 × 30 ml) and water (30 ml) and then dried ($MgSO_4$). Removal of solvent left an oil which slowly solidified. One crystallisation from hexane–CH_2Cl_2 gave pure N-*acetoxy*-N′N′-*pentamethylene*-N-*t-butylurea* as a colourless solid, m.p. 34—35 °C (2.95 g, 59%) (Found: C, 59.6; H, 9.2; N, 11.2. $C_{12}H_{22}N_2O_3$ requires C, 59.5; H, 9.15; N, 11.6%). This had $\nu_{max.}$ (Nujol) 1 768 and 1 690 cm^{-1}; δ 1.28 (s, 9 H, Bu^t), 1.62br (m, 6 H) and 3.65br (m, 4 H) [together $(CH_2)_5$], and 2.10 (s, 3 H, CH_3).

N-*Piperidinocarbonyl*-N-*t-butylhydroxylamine* (N-*hydroxy*-N′N′-*pentamethylene*-N-*t-butylurea*).—To the above urea (2.45 g) in ethanol (50 ml) was added $Ba(OH)_2 \cdot 8H_2O$ (2.5 g) and the mixture was stirred at room temperature for 3 h. Most of the ethanol was removed under reduced pressure, and the residue was distributed between water (25 ml) and ether (25 ml). The aqueous fraction was washed with two further portions of ether, and the ethereal extracts were combined and dried ($MgSO_4$), removal of solvent left a solid. This was crystallised from hexane–CH_2Cl_2 to give pure N-*hydroxy*-N′N′-*pentamethylene*-N-*t-butylurea* as a colourless solid, m.p. 137—138 °C (1.51 g, 75%) (Found: C, 60.0; H, 9.8; N, 13.7. $C_9H_{20}N_2O_2$ requires C, 60.0; H, 10.1; N, 14.0%). The product had $\nu_{max.}$ (Nujol) 3 320, 3 285, and 1 620 cm^{-1}; δ (after addition of a trace of hydrazobenzene to destroy nitroxide) 1.21 (s, 9 H, Bu^t), 1.55br (m, 6 H, $3CH_2$), 3.55br (m, 4 H, $2CH_2$), and 5.9br (s, 1 H, OH).

Piperidinocarbonyl t-Butyl Nitroxide.—The above *N*-hydroxurea was oxidised with alkaline $K_3Fe(CN)_6$ in ether. After separation and washing, the burgundy red ethereal solution was dried ($MgSO_4$) and the solvent removed to give the solid *nitroxide*; this crystallised from hexane as pale orange-red prisms, m.p. 38—39 °C (see Table 2).

Other Aminocarbonyl Nitroxides.—Following the above procedures, the following precursors to the morpholinocarbonyl and pyrrolidinocarbonyl nitroxides were prepared: O-*acetyl*-N-*morpholinocarbonyl*-N-*t-butylhydroxylamine* (85%), m.p. 69—70 °C (from hexane–CH_2Cl_2) (Found: C, 54.1; H, 8.5; N, 11.6. $C_{11}H_{20}N_2O_4$ requires C, 54.1; H, 8.25; N, 11.5%); N-*morpholinocarbonyl*-N-*t-butylhydroxylamine* (60%), m.p. 153—154 °C (from hexane–CH_2Cl_2) (Found: C, 53.4; H, 8.9; N, 13.8. $C_9H_{18}N_2O_3$ requires C, 53.45; H, 9.0; N, 13.85%); O-*acetyl*-N-*pyrrolidinocarbonyl*-N-*t-butylhydroxylamine*, m.p. 45.5 °C (from hexane–CH_2Cl_2) (Found: C, 57.5; H, 8.8; N, 12.4. $C_{11}H_{20}N_2O_3$ requires C, 57.9; H, 8.8; N, 12.3%); N-*pyrrolidinocarbonyl*-N-*t-butylhydroxylamine*, m.p. 148—149 °C (from hexane–CH_2Cl_2) (Found: C, 57.8; H, 9.8; N, 14.8. $C_9H_{18}N_2O_2$ requires C, 58.0; H, 9.7; N, 15.0%). The *N*-hydroxyureas were oxidised to the corresponding nitroxides by the usual procedure (see Table 2).

TABLE 4

Intermediates in the synthesis of alkanoyl t-butyl nitroxides

R	RCON(Bu^t)OAc M.p. (°C) [% yield]	% Found (Calc.) C	H	N	RCON(Bu^t)OH M.p. [% yield]	% Found (Calc.) C	H	N
Me	See footnote *							
$PhCH_2$	Oil (not purified)				85—86	69.3	8.2	6.6
						(69.6	8.2	6.8)
n-$C_{10}H_{21}$	Oil (not purified)				48	70.0	12.0	5.4
					[60] †	(70.0	12.1	5.4)
$PhCH_2CH_2$	79—80	67.5	8.0	4.9	74—75	70.8	8.6	6.2
	[67]	(68.4	8.0	5.3)	[95]	(70.6	8.7	6.3)

* Both products liquids (ref. 8). Hydrolysis of the *NO*-diacetyl-*N*-t-butylhydroxylamine under standard conditions gave the *N*-acetyl derivative in *ca.* 70% yield. † Yield based on *O*-acetyl-*N*-t-butylhydroxylamine.

Phenoxycarbonyl t-Butyl Nitroxide.—(a) *Acylation of phenol with* N-*acetoxy*-N-*t-butylcarbamoyl chloride.* To a stirred solution of the carbamoyl chloride (0.97 g) in methylene chloride (10 ml) was added phenol (0.47 g) followed by 4-dimethylaminopyridine (0.61 g). The mixture was stirred at room temperature for 15 h, diluted with ether (25 ml), and then washed with 2M-HCl (15 ml) and water (10 ml). The organic solution was dried ($MgSO_4$), solvent was removed, and the residue was distilled to give *phenyl* N-*acetoxy*-N-*t-butylcarbamate* as an almost colourless oil (1.14 g, 91%), b.p. 124—126 °C at 1.5 mmHg, which had $\nu_{max.}$ 1 805 and 1 740 cm^{-1}; δ 1.44 (s, 9 H, Bu^t), 2.19 (s, 3 H, CH_3), and 6.9—7.4 (m, 5 H, C_6H_5) (Found: C, 62.3; H, 7.2; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%).

(b) *Pyrrolidinolysis of phenyl* N-*acetoxy*-N-*t-butylcarbamate.* A solution of acetoxycarbamate (3.71 g) and pyrrolidine (1.325 g) in dry CH_2Cl_2 (10 ml) was stirred for 15 h at room temperature; any remaining pyrrolidine was removed by washing with 2M-HCl (2 × 10 ml) and water (10 ml) and then the CH_2Cl_2 solution was dried ($MgSO_4$). Removal of solvent left an oil (2.9 g) which was chromatographed on silica gel (180 g). Elution with CH_2Cl_2–ether (3 : 7) gave a yellow-brown semisolid (530 mg) as the first product eluted. Crystallisation of this from CH_2Cl_2–hexane gave *phenyl* N-*hydroxy*-N-*t-butylcarbamate*, m.p. 97—98 °C (450 mg, 18%), as a colourless solid. This had $\nu_{max.}$ 1 670 and 1 690 cm^{-1}; δ 1.48 (s, 9 H, Bu^t), 7—7.5 (m, 5 H, Ph), and 6.3br (s, 1 H, OH) (Found: C, 63.5; H, 7.6; N, 6.4. $C_{11}H_{15}NO_3$ requires, C, 63.1; H, 7.2; N, 6.7%). Further elution gave a second product (490 mg) identified as *N*-pyrrolidinocarbonyl-*N*-t-butylhydroxylamine.

Reaction of N-*t-Butylhydroxylamine with* 2,2,2-*Trichloroethyl Chloroformate.*—Trichloroethyl chloroformate (4.76 g) in dry benzene (5 ml) was slowly added to a stirred solution of *N*-t-butylhydroxylamine (2.0 g) and triethylamine (4.54 g) in benzene (15 ml), and the mixture was stirred for 2 h. Solvent was removed, and the residue was digested with hot hexane–CH_2Cl_2 (50 ml, 1 : 1). The triethylamine hydrochloride was removed, and solvent again removed to leave a waxy solid which was crystallised from hexane–CH_2Cl_2 to give N-*t-butyl*-O-(2,2,2-*trichloroethoxycarbonyl*)*hydroxylamine* (19) as a colourless solid, m.p. 74.5—75.5 °C (3.4 g, 58%). This had $\nu_{max.}$ (Nujol) 3 240 and 1 770 cm^{-1}; δ 1.23 (s, 9 H, Bu^t), 4.86 (s, 2 H, CH_2), and 6.4br (s, 1 H, NH) (Found: C, 31.8; H, 4.5; N, 5.35. $C_7H_{12}Cl_3NO_3$ requires C, 31.8; H, 4.6; N, 5.3%).

Benzyl Derivatives of N-*t-Butylhydroxylamine.*—(a) *Reaction of t-butylhydroxylamine with benzyl chloride.* A stirred mixture of t-butylhydroxylamine (4.6 g), benzyl chloride (6.6 g), and K_2CO_3 (7.5 g) in dry dimethyl sulphoxide (50 ml) was heated at 125 °C under N_2 for 2 h, cooled, and poured into water (100 ml). The resulting mixture was extracted with ether (3 × 50 ml) and the combined ether extracts were washed thoroughly with water (8 × 40 ml) and dried ($MgPO_4$). Removal of solvent gave crude N-*benzyl*-N-*t-butylhydroxylamine* as an oil which yielded colourless crystals, m.p. 71—72 °C from hexane (4.3 g, 46%, after purification). The product had $\nu_{max.}$ 3 600 and 3 540br; δ 1.14 (s, 9 H, Bu^t), 3.65 (s, 2 H, CH_2), 4.32br (s, 1 H, NH), and 7.05—7.30br (s, 5 H, C_6H_5) (Found: C, 74.2; H, 9.4; N, 7.4. $C_{11}H_{15}NO$ requires C, 73.7; H, 9.6; N, 7.8%).

(b) *Attempted reaction of the conjugate base of t-butylhydroxylamine with benzyl chloride.* t-Butylhydroxylamine (740 mg, 8.33 mmol) was added to a stirred suspension of sodium hydride (200 mg, 8.34 mmol) in dry tetrahydrofuran (25 ml), and the mixture was stirred for 5 min. To the thick white suspension which formed was added freshly distilled benzyl chloride (890 mg, 7.03 mmol), and the mixture was then refluxed for 18 h. Water was added dropwise to the cooled mixture, until the white precipitate had dissolved, and the organic layer was then washed with saturated aqueous NaCl (3 × 5 ml) and dried ($MgSO_4$); solvent was removed to give a pale yellow oil (1.12 g) which appeared (n.m.r.) to contain t-butylhydroxylamine, its *N*-benzyl derivative, benzyl chloride, and an additional product, possibly the desired *O*-benzyl derivative. Dissolution of the oil in ether followed by extraction into acid removed the benzyl chloride, and after basification and re-extraction into ether a mixture of the three basic components (660 mg) was obtained as a colourless liquid. The major components of this (>90 mol%) were the *N*- and supposed *O*-benzyl derivatives (2 : 1) readily separable by t.l.c. (EtOAc–PhH, 2 : 1). The minor product had $\nu_{max.}$ 3 240 cm^{-1}; δ 1.06 (s, 9 H, Bu^t), 4.6 (s, 2 H, CH_2), and 7.20 (s, 5 H, C_6H_5), identical with authentic O-*benzyl*-N-*t-butylhydroxylamine* prepared as below.

(c) *Preparation of* O-*benzyl*-N-*t-butylhydroxylamine.* (i) To a stirred solution of *O*-acetyl-*N*-t-butylhydroxylamine (11.79 g) and pyridine (10.67 g) in dry benzene (25 ml) was added 2,2,2-trichloroethyl chloroformate (19.1 g) and the mixture was boiled under reflux for 6 h; it was cooled, diluted with ether (50 ml), and washed with 2M-HCl (2 × 40 ml) and water (20 ml), and dried ($MgSO_4$). Removal of solvent left crude O-*acetyl*-N-*t-butyl*-N-*trichloroethoxycarbonylhydroxylamine* as a brown oil (20.7 g) which had $\nu_{max.}$ 1 804, 1 775, and 1 730 cm^{-1}; δ 1.37 (s, 9 H, Bu^t), 2.04 (s, 3 H, CH_3), and 4.58 (s, 2 H, CH_2). (ii) This oil (20 g) in ethanol (50 ml) was hydrolysed by the usual procedure with $Ba(OH)_2 \cdot 8H_2O$ (12 g) to give N-*t-butyl*-N-*trichloroethoxycarbonylhydroxylamine* (8.4 g), obtained as colourless needles, m.p. 75—77 °C from hexane (8.4 g), having $\nu_{max.}$ 3 560, 3 380, 1 728, and 1 695 cm^{-1}; δ(CCl_4) 1.45 (s, 9 H, Bu^t), 4.75, (s, 2 H, CH_2), and 6.35br (s, 1 H, OH) (Found: C, 32.1; H, 4.7; N, 5.55. $C_7H_{12}Cl_3NO_3$ requires C, 31.8; H, 4.6; N, 5.3%). (iii) The above product (8.1 g) in dry dimethoxyethane (25 ml) was treated with sodium hydride (0.74 g) and the mixture was stirred for 10 min. Benzyl bromide (5.23 g) was added and the mixture was stirred for 15 h; it was then diluted with ether (50 ml), washed with 2M-HCl (2 × 20 ml) and water (20 ml), and dried ($MgSO_4$). Removal of solvent gave O-*benzyl*-N-*t-butyl*-N-*trichloroethoxycarbonylhydroxylamine* (8.6 g) as colourless crystals, m.p. 69—71 °C (from hexane–CH_2Cl_2) having $\nu_{max.}$(Nujol) 1 722 cm^{-1}; δ 1.41 (s, 9 H, Bu^t), 4.75 and 4.88 (both, s, 4 H, 2 CH_2), and (s, 5 H, C_6H_5) (Found: C, 47.3; H, 5.0; N, 4.1. $C_{14}H_{18}Cl_3NO_3$ requires C, 47.4; H, 5.1; N, 3.95%). (iv) The above product (6.15 g) in glacial acetic acid (15 ml) was stirred with zinc dust (5 g) at room temperature for 15 h. The mixture was then filtered, and the solution basified with aq. NaOH, and the organic products were extracted with ether (3 × 25 ml). The ether extract was dried and extracted into 2M-HCl (2 × 15 ml). This acidic solution was basified, extracted with ether (3 × 15 ml), and the ether solution was dried ($MgSO_4$) and distilled to yield O-*benzyl*-N-*t-butylhydroxylamine* as a pale yellow oil, b.p. 75—76 °C at 5 mmHg (2.93 g), having $\nu_{max.}$(neat) 3 240 cm^{-1}; δ 1.06 (s, 9 H, Bu^t), 4.52 (s, 1 H, NH), 4.6 (s, 2 H, CH_2), and 7.20 (s, 5 H, C_6H_5)

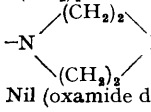
(Found: C, 73.9; H, 9.75; N, 8.0. $C_{11}H_{15}NO$ requires C, 73.7; H, 9.6; N, 7.8%).

(d) *Preparation of* N-*t-butyl*-O-*tritylhydroxylamine*. Triphenylchloromethane (1.57 g) was added to a stirred solution of *N*-t-butylhydroxylamine (0.5 g) and triethylamine (0.8 ml) in dry dimethylformamide (3 ml) under N_2. The mixture was stirred for 15 h at room temperature and then distributed between ether and water. The ether solution was washed with water (×3), dried ($MgSO_4$), and solvent was removed to give a yellow oil which slowly crystallised. Crystallisation from ethanol gave N-*t-butyl*-O-*tritylhydroxylamine* (1.51 g), m.p. 82—83 °C, having $\nu_{max.}$ 3 220 cm^{-1} (NH); δ 0.8 (s, 9 H, Bu^t), 4.5br (s, 1 H, NH) and 7.1—7.5 (m, 15 H, 3Ph) (Found: C, 83.8; H, 7.8; N, 4.7. $C_{23}H_{25}NO$ requires C, 83.3; H, 7.6; N, 4.2%).

Preparation of Acyl Nitroxide Biradicals.—The general procedures outlined for the synthesis of monoradicals using *O*-acetyl-*N*-t-butylhydroxylamine as the key starting point were adapted for the synthesis of biradicals commencing with terephthaloyl, isophthaloyl, and adipoyl chlorides.

TABLE 5

Intermediates in the synthesis of acyl nitroxide biradicals

M	$[AcO(Bu^t)NCO]_2M$ M.p. (°C) [% yield]	% Found (Calc.) C	H	N	$[HO(Bu^t)NCO]_2M$ M.p. (°C) [% yield]	% Found (Calc.) C	H	N
p-(−C_6H_4−)	126—128 [44]	61.1 (61.2	7.1 7.2	6.9 7.1)	190 (decomp.) * [90]	62.3 (62.3	7.8 7.85	8.9 9.1)
m-(−C_6H_4−)	92—93 [51]	61.3 (61.2	7.0 7.2	7.2 7.1)	176—177 [33]	62.7 (62.3	7.7 7.85	8.7 9.1)
−$(CH_2)_4$−	76 [67]	58.4 (58.0	9.9 8.7	7.55 7.5)	151—152 [44]	58.3 (58.3	9.7 9.8	9.5 9.7)
	196—197 [53]	53.8 (54.0	8.0 8.1	13.9 14.0)	240 (decomp.) † [80]	53.45 (53.1	9.0 8.9	17.9 17.7)
Nil (oxamide derivatives)	136—137 [80]	53.1 (53.2	7.6 7.7	8.6 8.9)	233—234 (decomp.) [77]	51.7 (51.7	8.8 8.7	11.9 12.1)

* Oxidation gave biradical (22), m.p. 84—85 °C (from benzene) (Found: C, 63.1; H, 6.9; N, 8.4. $C_{16}H_{22}N_2O_4$ requires C, 62.7; H, 7.2; N, 9.1%). † Oxidation gave *biradical* (23), m.p. 135—136 °C (from hexane–CH_2Cl_2) (Found: C, 53.4; H, 8.3; N, 17.6. $C_{14}H_{26}N_4O_4$ requires C, 53.5; H, 8.3; N, 17.8%).

Similarly the formation of a bis(aminocarbonyl nitroxide) from piperazine followed the general procedure described for piperidine, except that care was taken to use two equivalents of the carbamoyl chloride to one of dry piperazine, and a small excess over two equivalents of pyridine, instead of using excess of the secondary amine. Data for the intermediates in these preparations are recorded in Table 5.

Unsuccessful Approaches to Biradicals.—(a) *From o-phthaloyl chloride*. *o*-Phthaloyl dichloride reacted with *O*-acetyl-*N*-t-butylhydroxylamine in the normal way to give 1,2-*bis*-(N-*acetoxy*-N-*t-butylcarbamoyl*)*benzene* (47%), m.p. 80—81 °C, $\nu_{max.}$ (Nujol) 1 800 and 1 670 cm^{-1}; δ 1.53 (s, 18 H, $2Bu^t$), 1.80 (s, 6 H, $2CH_3$), and 7.35 (s, 4 H, C_6H_4) (Found: C, 61.3; H, 7.1; N, 7.1%). Hydrolysis under normal conditions gave 3-*t-butyl*-2,3-*benzoxazine*-1,4-*dione* (25), m.p. 64—66 °C from ethanol (60%), which had $\nu_{max.}$ (Nujol) 1 740 and 1 660 cm^{-1}; δ 1.70 (s, 9 H, Bu^t) and 7.7—8.4 (m, 4 H, C_6H_4) (Found: C, 65.7; H, 6.00; N, 6.1. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%). This product was also obtained in excellent yield by boiling under reflux for 24 h a solution of *o*-phthaloyl dichloride (4.57 g), triethylamine (4.57 g), and *N*-t-butylhydroxylamine (2 g) in dry ether (100 ml).

(b) *From succinoyl chloride*. Following the normal procedure with *O*-acetyl-*N*-t-butylhydroxylamine, only 2-*t-butyl*-1,2-*oxazine*-3,6-*dione* (24) could be isolated, m.p. 141—142.5 °C, $\nu_{max.}$ (Nujol) 1 795 and 1 672 cm^{-1}; δ 1.38 (s, 9 H, Bu^t) and 2.8 (s, 4 H, $2CH_2$) (Found: C, 56.1; H, 8.2; N, 8.05. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.65; N, 8.2%).

Preparation of 4,4-*Dimethyloxazolin*-2-*one* N-*Oxyl*.—(a) *Reduction of* 2-*methyl*-2-*nitropropan*-1-*ol*. Following a procedure reported for the reduction of 2,3-dimethyl-2,3-dinitrobutane, a stirred solution of 2-methyl-2-nitropropanol (11.9 g) in aqueous ethanolic NH_4Cl (5 g in 100 ml 50%) was treated with acid-washed zinc dust (20 g) during 3 h, the temperature being kept below 15 °C. The mixture was stirred for 3 h at room temperature and then filtered; the solids were washed with water (4 × 25 ml). The combined filtrate and washings were acidified to pH 2 with conc. HCl (*ca.* 6.5 ml) and most of the solvent was then removed under reduced pressure to give a syrup to which was added K_2CO_3 (40 g). The resulting mixture was extracted by $CHCl_3$ in a Soxhlet apparatus for 4 h. Removal of chloroform from the extract left a viscous oil which was mixed with an equal volume of fresh chloroform. Crystals slowly separated (3.73 g) and after crystallisation from hexane–$CHCl_3$ pure 2-(*N-hydroxyamino*)-2-*methylpropan*-1-*ol* was obtained as colourless hygroscopic crystals, m.p. 62—64 °C (Found: C, 45.1; H, 10.1; N, 12.8. $C_4H_{11}NO_2$ requires C, 45.6; H, 1055.; N, 13.3%).

(b) *Reaction of* 2-(N-*hydroxyamino*)-2-*methylpropan*-1-*ol with phosgene*. A solution of phosgene in toluene (4 ml, 12.5%) was added dropwise to a stirred and cooled (ice) suspension of K_2CO_3 (2.1 g) in acetonitrile (8 ml) containing the above hydroxylamine (0.53 g). The mixture was stirred for 45 min at room temperature, filtered through a bed of K_2CO_3, and the solvent was evaporated to leave an oil. Examination by t.l.c. revealed at least five components, one of which (R_F 0.6 using 5% MeOH–20% EtOAc–75% CH_2Cl_2) appeared to be a major product. This product was isolated by preparative t.l.c. (44%) and crystallised from hexane–$CHCl_3$ to give 3-*hydroxy*-4,4-*dimethyloxazolin*-2-*one*, as colourless needles, m.p. 76—78 °C, having $\nu_{max.}$ 3 250br and 1 755; δ 1.3 (s, 6 H, 2Me), 4.05 (s, 2 H, CH_2), and 8.0br, (s, 1 H, OH) (Found: C, 45.7; H, 6.9; N, 10.85. $C_5H_9O_3N$ requires C, 45.8; H, 6.9; N, 10.7%).

(c) *Oxidation of the* N-*hydroxyoxazolinone*. The above product (30 mg) in benzene (5 ml) was stirred with nickel peroxide (100 mg) and Na_2SO_4 (20 mg) to give a peacock blue solution; t.l.c. showed the presence of a single (blue) product which, on removal of solvent, had $\nu_{max.}$ 1 800 cm^{-1}. Dilution with benzene and examination by e.s.r. showed a

major paramagnetic species with a_N 7.52 G consistent with the 4,4-dimethyloxazolin-2-one *N*-oxyl structure, together with a second, minor species having a_N = 14.5 G. When a dilute solution of the *N*-hydroxy-compound was oxidised by t-butyl hyponitrite, the second radical was not detected.

(d) *Decomposition of the radical.* A solution of the radical in CCl_4 (*ca.* 5%) was left at room temperature overnight, after which the colour had changed to blue-green, an i.r. absorption at 1 630 cm^{-1} (–N=O?) had appeared, and some eight decomposition products were present (t.l.c.) in addition to unchanged radical.

We thank the S.R.C. (P. F. A., T. C. J., and P. W.) and Chelsea College (S. A. H. and N. P. Y. S.) for grants in support of this work, and Dr. A. R. Forrester for valuable comments.

[7/2038 *Received* 21*st November*, 1977]