Nitroxide Radicals. Part 20.[1] Formation and Reactions of t-Butyl *p*-Formylphenyl Nitroxide and its Derivatives

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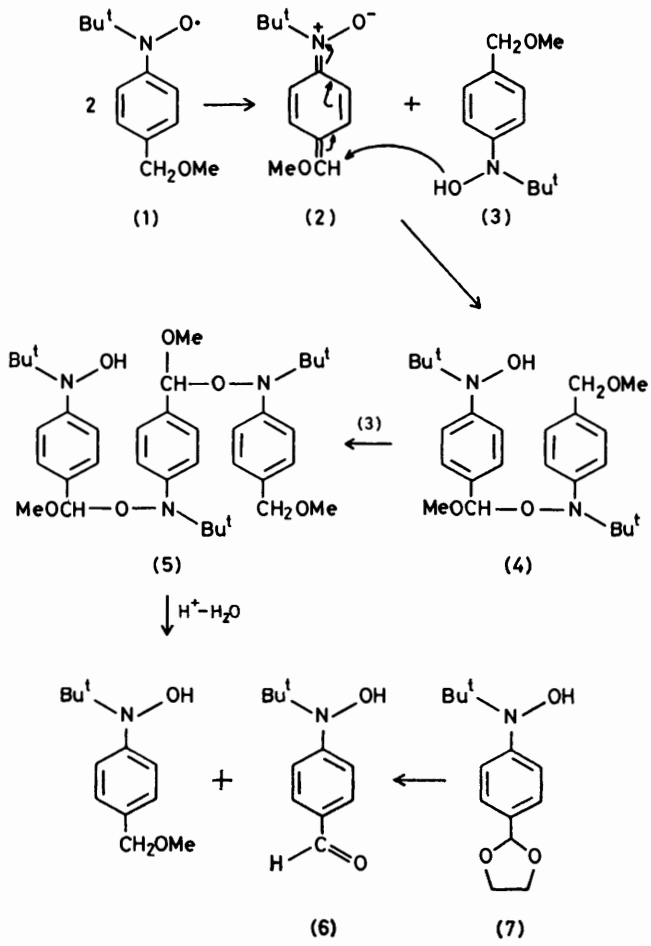
Preparation of the parent hydroxylamine of the title nitroxide and its conversion into several hydroxylamine derivatives and the corresponding nitroxides has been achieved with a view to using functionalised aryl nitroxides as spin labels. The a_N values of the derived aryl nitroxides vary with the nature of their *para*-substituents, thus providing a potential method for identifying the site of attachment of aryl nitroxide spin labels.

Reactions of a nitrone-nitroxide, derived from the title radical, with cyanoisopropyl, phenyl, benzoyloxyl, and t-butoxyl radicals were investigated. In no case was a bisnitroxide formed.

THE development of spin labelling [2] during the last decade has led to major advances in the study of biological systems. Usually, the labels are cyclic di-t-alkyl nitroxides bearing a functional group remote from the $>N-O\cdot$ group. The site(s) of attachment is assumed from the known reactivities of the functional groups in the biological system and the label. There is no direct spectroscopic method by which this can be confirmed, or indeed which would indicate whether attachment has occurred at more than one type of site, since the easily measured parameters a_N and g of the label vary little with the nature of the binding linkage. By comparison, the a_N values of aryl nitroxides vary with the nature and position of their ring substituents,[3] and Hammett relationships [4] have been established in several cases. Aryl nitroxides have been little investigated as spin labels, mainly because they are usually shorter-lived than di-t-alkyl nitroxides and few bearing a functional group have been isolated. We have begun an investigation of the potential use of substituted aryl nitroxides as spin labels and report here on initial work with t-butyl *p*-formylphenyl nitroxide (8).

RESULTS AND DISCUSSION

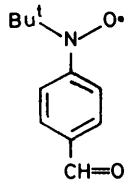
We had previously isolated [5] the hydroxylamine precursor (6) of the aforementioned nitroxide from the decomposition products of t-butyl *p*-tolyl nitroxide, but the yield was poor and the method was not suitable for preparative purposes. Better yields were obtained by acid-catalysed hydrolysis of the decomposition products of the *p*-methoxymethylphenyl nitroxide (1). This gave a mixture of two hydroxylamines, (4) and (5). The reaction is considered to proceed as indicated in the Scheme, support for which was obtained by examination of the product mixture before hydrolysis. This consisted mainly of two hydroxylamines (t.l.c., tetrazolium test).[6] The average molecular weight (500 ± 25) (osmometric) and ratios of the integrals of the n.m.r. signals at δ 1.06, 1.14 (Bu^t), 3.2—3.5 (MeO), 4.4 (CH_2), 5.53 (OC*H*OMe), and 7.2—7.4 (Ar-H) were consistent with the product mixture being composed of dimer (4) and trimer (5) in the ratio 2 : 1. The nitroxides obtained from these separated hydroxylamines showed in their e.s.r. spectra, in addition to aryl proton splittings, coupling to only one other proton $a_H = 1.9$ G. Also, the a_N values (both 13.0 G) were considerably larger than that of the starting nitroxide indicating that the *para*-substituent had been substantially modified. The Scheme is analogous to that proposed [5] for decomposition of *p*-alkylphenyl t-butyl nitroxides and the hydrolysis step predictably yields both starting hydroxylamine and (6). Interestingly the corresponding phenoxyl (9) with Fremy's salt also yields a *p*-formyl radical, presumably by an analogous route.[7] The *p*-formylphenylhydroxylamine (6) was also produced by hydrolysis of the acetal hydroxylamine (7), the latter being prepared by standard



SCHEME 1

methods, but yields were less reproducible by this method.

*Derivatives of t-Butyl-*p*-formylphenylhydroxylamine.*—Condensation of the aldehyde (6) with several alkyl- and aryl-amines and one amino-ester proceeded without difficulty to give the crystalline imines (11). Reaction



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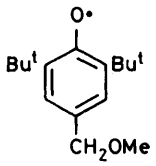

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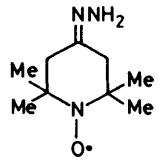

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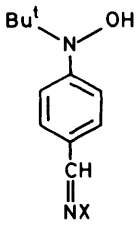

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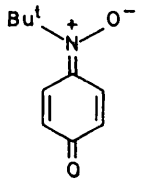
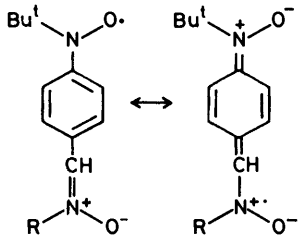


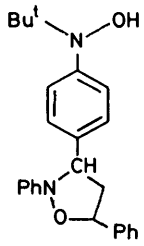
(12)

with *m*- and *p*-phenylenediamines gave rather insoluble dihydroxylamines and with *o*-phenylenediamine a mixture of products the composition of which depended on the conditions. This reaction is still under investigation.

The aldehyde also yielded an oxime (11; X = OH) and a hydrazone (11; X = NH_2) but repeated attempts to produce the azine and an unsymmetrical azine from the hydrazone (10) failed. *N*-t-Butyl- and phenylhydroxylamines readily gave the corresponding nitrones, but the latter could not be generated from the imine (11; X = Ph) and *m*-chloroperbenzoic acid. Instead, the quinone imine *N*-oxide (12) was the main product. However, the nitrone-nitroxide (13; R = Ph) may well



(13a) (13b)



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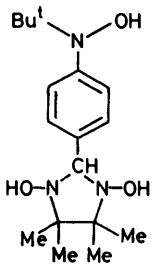

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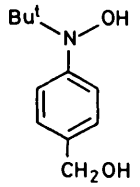
be an intermediate, since it also gives the quinone imine *N*-oxide (12) with *m*-chloroperbenzoic acid. Cycloaddition of styrene to the hydroxylamine precursor of the nitroxide (13; R = Ph) gave the isoxazolidine (14), the orientation of addition being confirmed by n.m.r. measurements.[8] Condensation of the formyl-hydroxylamine (6) with 2,3-bis(hydroxylamino)-2,3-dimethylbutane[9] yielded the sparingly soluble trihydroxylamine (15).

Preferential hydrogenation of the formyl group of (6) occurs over platinum and the resulting primary alcohol (16) was esterified by reaction with 3,5-di-t-butyl-4-hydroxybenzoyl chloride. Acylation occurred mainly at the N–OH group since the principal CH_2 signal in the n.m.r. spectrum of the mixture was at δ 4.55. The minor product (17) absorbed at 1 712 cm^{-1} in the i.r. and showed a CH_2 resonance at δ 5.31.

E.S.R. Spectra of Mononitroxides.—The hydroxylamines were converted into the corresponding nitroxides by reaction with silver oxide in carbon tetrachloride. The *p*-imino-nitroxides from (11; X = alkyl or aryl), which were readily hydrolysed to the corresponding aldehyde, were separated by chromatography. Only the nitroxides (13) with a *para*-nitrone group were sufficiently long-lived to be isolated. Interestingly these were green.



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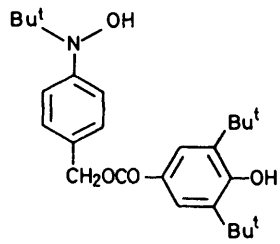

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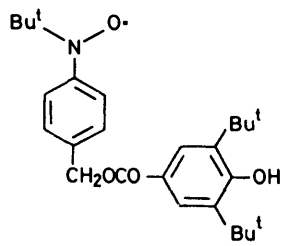

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The gradation in a_N value of the nitroxides with *para*-substituents, $-CH_2Me > -CH_2N< > -CH_2O > -CH<^{O-}_{O-}$, reflects the increasing electronegativities of the atoms attached to benzylic carbon. Also, the a_N values of nitroxides with *para*-substituents $-CH{=}N-alkyl > -CH{=}N-aryl > -CH{=}\overset{+}{N}(\bar{O})-alkyl > CH{=}O > CH{=}\overset{+}{N}(\bar{O})-Ar$ decrease in the order given, indicating that the nitrone group and the formyl group have similar electron-withdrawing properties. These effects can be quantified of course by means of a Hammett plot; this has been done previously for several series of nitroxides.[4] Using a_N values (carbon tetrachloride) previously reported from this laboratory [3,5] for t-butyl aryl nitroxides *para*-substituted with Bu^t, Et, Cl, Br, I, F, Pr^i, PhO, and MeO, and literature [10] σ^+ values the relationship a_N =

TABLE 1

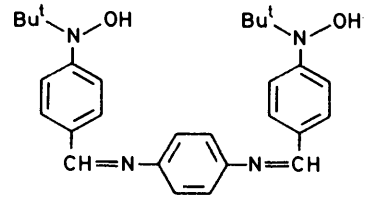
Hyperfine coupling constants of aryl t-butyl nitroxides [a] (29)

R	a_N	$a_{o\text{-}H}$	$a_{m\text{-}H}$	a_H^{CH}	$a_N^{CH=N}$	a_H^R	σ^+ Derived
Et	12.45	1.95	1.0			a_H^{CH} = 1.90	
H	12.30	2.05	1.0			$a_{p\text{-}H}$ = 2.05	
$CH_2OCOC_6H_2Bu^t_2OH$	12.15	1.90	0.85			$a_H^{CH_2}$ = 1.60	0.005
1,5-Diphenylisoxazol-3-yl	12.15	2.2	1.25			a_H^{CH} = 0.95	0.005
CH_2OH	12.10	1.85	0.95			$a_H^{CH_2}$ = 1.85	0.03
CH_2OMe	12.10	1.85	0.95			$a_H^{CH_2}$ = 1.83	0.03
1,3-Dioxolan-2-yl	12.05	2.1	1.05			a_H^{CH} = 1.05	0.08
$CH{=}NBu^t$ [c]	11.8						0.33
$CH{=}NCHPhCO_2Et$ [b]	11.25	2.2	1.05	1.05	1.30	a_H^{NCH} = 0.4	0.88
CH=NOH	11.2	2.2	0.85	0.85	0.85		0.93
CH=NPh	11.0	2.2	1.0				1.13
$CH{=}NC_6H_4Bu\text{-}p$	11.0	2.2	0.9				1.13
$CH{=}NC_6H_4OH\text{-}p$ [c]	10.8						1.33
$CH{=}\overset{+}{N}(\bar{O})Bu^t$	10.8	2.25	1.15	1.15	1.15		1.33
CHO	10.65	2.2	0.9				
$CHNNH_2$	10.6	2.3	0.9				1.535
$CH{=}\overset{+}{N}(\bar{O})Ph$	10.5	2.35	1.18	1.18	1.18		1.635

[a] All measurements in carbon tetrachloride. [b] Simulation of spectrum imperfect; these values give best fit. [c] Broad lines prevented resolution of this spectrum.

$-1.68\sigma + 12.14$ (correlation coefficient, $R = 0.89$) was derived. A poorer fit of the data was achieved with σ values. From the above relationship and the a_N values in Table 1, σ^+ values can be conveniently evaluated for the less common groups such as CH=NBu^t, literature values for which are not readily available. Several σ^+ values derived in this way are listed in Table 1. Conversation of the formyl group in (8) into a formimidoyl group in (29; R = CH=NBu^t and R = CH=NCHPh-CO_2Et) results in a 5—10% increase in the value of a_N. Hence attachment of the nitroxide (8) to, for example, a free amino-group in a protein would be easily detectable from the relative change in the a_N value. It is in this direction that the work will proceed.

Diradicals.—Treatment of the di-imine (19) with a small amount of silver oxide gave the corresponding monoradical ($a_N = 11.15$, $a_{o\text{-}H} = 2.3$, $a_{m\text{-}H} = 0.85$ G). The relatively large line-width prevented evaluation of $a_N^{CH=N}$ and $a_H^{CH=N}$. When an excess of silver oxide was employed a spectrum with five bands of lines was detected, consistent with that of the diradical[11] (20) with $J > a_N$. However, the band intensities 1.0 : 1.5 : 2.7 : 1.4 : 1.0 did not correspond to these predicted by theory, *i.e.* 1 : 2 : 3 : 2 : 1. Further, only bands 1, 3, and 5 displayed fine structure. This may be due to (*a*) an alternating line-width effect, the result of modulation of the exchange interaction between two radical centres by some time-dependent molecular motion, most probably rotation of the nitroxide groups around the C(aryl)–N bonds; (*b*) the presence of formyl nitroxide (8); or (*c*) a combination of (*a*) and (*b*). Some hydrolysis of the bisnitroxide (20) to the formyl nitroxide (8) occurs on chromatographic adsorbents and it was not possible to exclude the latter in this way nor to establish its formation, albeit in small amount, during oxidation with metal oxides. Diradicals with $J > a_N$ should show nitrogen and proton splittings equal to $a/2$ where a is the appropriate coupling constant of the corresponding monoradical.[11] Hence, a diradical spectrum ($J > a$) was computed using splittings derived from the monoradical and a linewidth of 0.6 G. Comparison with the spectrum of the formyl nitroxide showed clearly that the splittings on bands 1, 3, and 5 of the actual diradical spectrum must be due to the formyl nitroxide.



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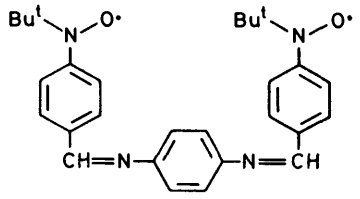

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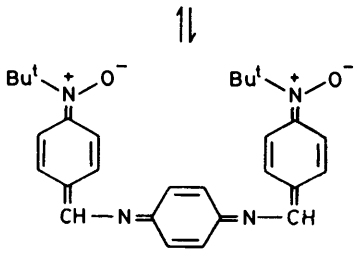
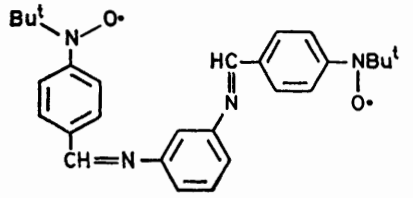


(20b)

Oxidation of the *meta*-phenylenebishydroxylamine with lead dioxide gave the corresponding bisnitroxide (21), whose spectrum showed five bands ($J > a_N$ = *ca.* 10.75 G) in the ratio 1.0 : 0.84 : 2.5 : 0.8 : 1.0. Hyperfine structure was evident on bands 1, 3, and 5, again due

to the formyl nitroxide (8). The monoradical (a_N = 11.25; $a_{o\text{-}H}$ — 2.1; $a_{m\text{-}H}$ — 1.0; $a_H^{CH=N} + 2a_N^{CH=N}$ = 2.2 G) was most conveniently generated by mixing equimolar amounts of bisnitroxide (21) and the corresponding dihydroxylamine.



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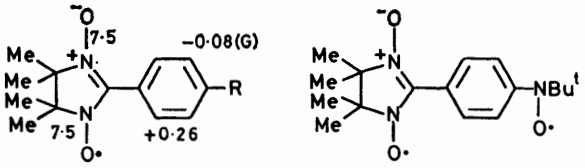


(22) (23)

Dreiding models indicated that in both diradicals the nitroxide groups can approach to within 1—2 Å making direct exchange interaction [12] possible. A glass spectrum (toluene) showing D = 140 G was easily obtained at —160 °C from the *meta*-bisnitroxide. Using the point-dipole approximation [13] this corresponds to an average separation of the unpaired electrons (r) = 5.85 Å. Repeated attempts to obtain a similar spectrum from the *para*-isomer failed. From neither binitroxide was a $\Delta M_s = 2$ transition observed.

The *para*-isomer, unlike the *meta*-isomer, could of course exist in a diamagnetic form (20a ⇌ 20b) (note that these are not mesomers since they have different numbers of unpaired electrons) but it would seem that at room temperature in solution, conformational preferences which prevent conjugation of the radical centres must be highly populated. When the solution was heated to 80 °C the five-band spectrum persisted and there was no substantial change in the relative intensities of the bands. At —40 °C the spectrum weakened and at —80 °C almost disappeared. This observation, together with the failure to obtain a glass spectrum at low temperature, suggests that the diamagnetic form (20b) is the ground state and the diradical (20a) is the more energetic state.

Oxidation of the trihydroxylamine (15) suspended in carbon tetrachloride with silver oxide or nickel peroxide gave a mixture of light blue and purple radicals, the relative amounts depending upon the amount of oxidant and the oxidation time. These were easily separated chromatographically. The light blue radical had an e.s.r. spectrum ($2a_N$ = 7.5 G) similar to that of the 2-phenylnitronyl nitroxide (22; R = H) and is assigned the nitronyl nitroxide structure (22; R = Bu^{t}NOH).

The purple radical gave the relatively complex spectrum shown in the Figure and a well-defined $\Delta M_s = 2$ transition at 1 580 G. For a diradical Å–B̈ the coupling constants of protons in the A moiety are approximately equal to the arithmetic sum of the coupling constants of the corresponding A protons in the monoradicals Å–B and A–B̈ and likewise for the B protons.[1] Accordingly using known values for the coupling constants [9] of the 2-phenylnitronyl nitroxide (22) and the *p*-nitrone-nitroxide (13; R = Bu^t) predicted values for the bisnitroxide (23) were calculated (Table 2). Only slight modifications of

TABLE 2

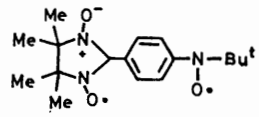
Predicted and actual values of coupling constants (G) for bisnitroxide (23)

	Predicted	Actual
a_N	10.8	10.8
a_N	8.06 *	8.0
a_N	8.06 *	8.0
$a_{o\text{-}H}$	2.32	2.4
$a_{p\text{-}H}$	1.38	1.5

* The $a_{O=\overset{+}{N}(\bar{O})}$ value of 1.12 G for (22; R = H) is divided over the two ring nitrogens in (23).

these values were required before a computational fit with the experimental spectrum was obtained. The experimental and computed spectra are shown in the Figure.

A weak glass spectrum was obtained in toluene at —160 °C which clearly showed two dipolar splittings (D = 191 and 115 G) and possibly a third very weak one. Hence, the bisnitroxide (23) had been frozen into at



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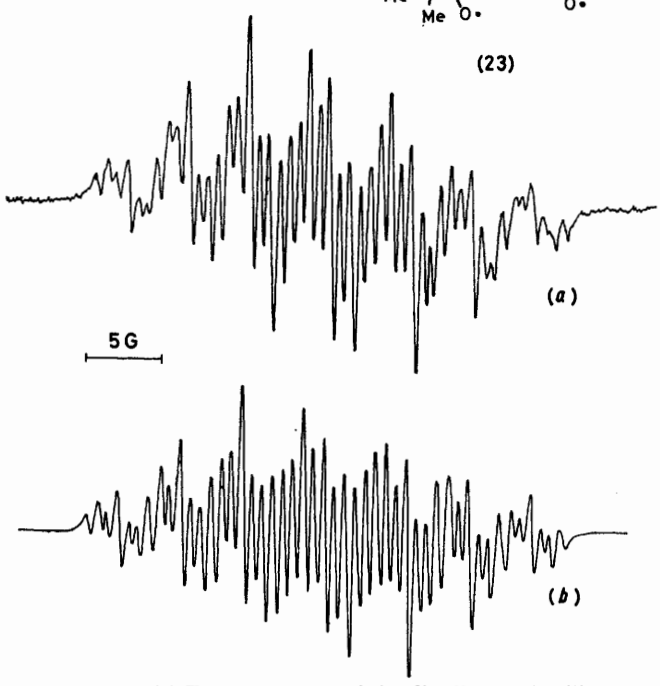
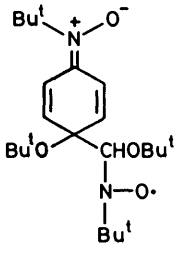


FIGURE (*a*) E.s.r. spectrum of the diradical (23); (*b*) computer simulation of the e.s.r. spectrum

least two different conformations, the D values corresponding to average separations of the unpaired electrons of 5.25 and 6.25 Å. These values are significantly smaller than the shortest distance of 6.72 Å (models) between the >N–O· groups (mid-points of the N–O bonds). This difference presumably reflects the extensive unpaired electron delocalisation in this unsymmetrical bisnitroxide.

Symmetrical diradicals such as bisnitroxides [11] and bisphenoxyls [3] are well-known but unsymmetrical diradicals, especially those in which the mono-radical components have significantly different g values, are rare. Indeed only one phenoxyl-nitroxide [14] diradical has been reported and even this assignment is doubtful. The phenolic hydroxylamine (17) was structurally designed to provide the first unambiguous example of such a diradical and its oxidation was investigated with this aim.

The phenolic hydroxylamine (17) was treated with a variety of metal oxide oxidants [silver(II), lead(II), or nickel (peroxide)], initially with small amounts and then with an excess. In each case, the spectrum of the corresponding t-butyl aryl nitroxide (a_N = 12.15, $a_{o\text{-}H}$ = 2.15, $a_{m\text{-}H}$ = 0.90, a_{CH_3} = 1.45 G) was the only radical detected although under these conditions the related



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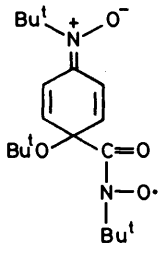

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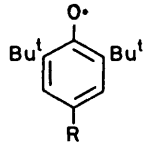

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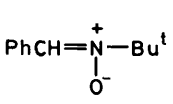

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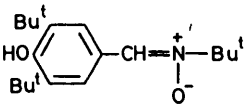

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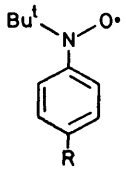

(29)

phenol (26; R = CH_2Ph) gave intense spectra of the corresponding phenoxyl ($a_{m\text{-}H}$ = 2.1, $a_H^{CH_3}$ = 0.55 G). Further, no diradical glass spectrum could be obtained when the toluene solution was frozen to −160 °C.

Successive additions of lead tetra-acetate to a solution of the nitroxide (18) lead to a weakening and distortion of the components of the nitrogen triplet and the slow emergence of a phenoxyl spectrum ($a_{m\text{-}H}$ = 2.12 G). Eventually only the phenoxyl spectrum remained. Occasionally during this process the solution was frozen, but at no time was a diradical spectrum detected.

Preferential initial formation of the nitroxide is understandable after consideration of the bond strengths of hydroxylamines and phenols.[15] For hydroxylamines D(OH) is *ca.* 70 kcal mol^{-1} while D(OH) for the phenol (26; R = Bu^t) is 81.2 kcal mol^{-1}. Our results indicate that not only is the hydroxylamine more easily oxidised than the phenol but so also is the nitroxide. Radicals (nitroxides, phenoxyls) and nucleophiles (hydroxylamines, phenols) would react readily with the ensuing quinone methide imine *N*-oxide giving nitroxides or hydroxylamines,[5] themselves capable of being further oxidised. Unfortunately it was not possible to assign structures to the nitroxides giving rise to the continuously changing spectra, since the components of the nitrogen triplet were invariably unsymmetrical. Only when the sequence of nitroxides was exhausted did formation of phenoxyl become obvious. This explanation is not of course unique and alternatives involving rapid nitroxide–phenoxyl or phenoxyl–phenoxyl (O–C) coupling cannot be excluded on the evidence. In any event, the presence of benzylic hydrogens in the nitroxide moiety was a structurally undesirable feature for our purpose.

The ready addition of a wide variety of radicals to nitrones to give nitroxides makes the *para*-nitronyl nitroxide (13; R = Bu^t) a useful potential source of unsymmetrical bisnitroxides. Accordingly, the nitroxide (13; R = Bu^t) was treated with several radical initiators and the ensuing reactions monitored using e.s.r. measurements.

(a) *Azobisisobutyronitrile* (*AIBN*). AIBN (7 mol) was added to the nitrone-nitroxide (13; R = Bu^t) (1 mol) in carbon tetrachloride and the solution was warmed to 70 °C for 5—6 min. On cooling to room temperature no significant decrease in the nature or intensity of the e.s.r. spectrum was observed. Re-heating and/or addition of more AIBN was without effect. Repetition of the experiment using t-butyl biphenyl-4-yl nitroxide in place of (13; R = Bu^t) gave a similar result. However, when the nitrone (27) was similarly treated the expected triplet of doublets (a_N = 13.8, a_H = 2.15 G) was easily detected.

Failure of 2-cyanoisopropyl radicals to react at the >N–O· groups of the nitroxides is presumably due to steric protection by the flanking t-butyl group. The apparent unreactivity of the nitrone group was more surprising especially in view of the result with the nitrone (27). However, phenyl t-butyl nitrone (27) is not a particularly efficient trap for t-alkyl radicals [15] and we surmise that the nitrone group of (13) is even less reactive because it is perturbed by conjugation with the

nitroxide group (13a) ⟷ (13b). Significantly, di-radicals were not detected when the bifunctional phenolic nitrone (28) was used to trap C- and O-centred radicals.[16]

(b) *Benzoyl peroxide.* Addition of benzoyl peroxide (5 mol) to a solution of the nitrone-nitroxide (13; R = Bu^t) (1 mol), followed by heating and then cooling to room temperature, again caused only a slight decrease in the intensity of the spectrum. This process had to be repeated several times before a distortion in the relative intensities of the lines became obvious. Further additions eventually led to major changes but the resulting spectra, which were weak, complex, and unsymmetrical, defied analysis. Benzoloxyl radicals add readily to t-butyl phenyl nitrone (27) to give the corresponding nitroxide[17] (a_N = 12.7, a_H = 1.4 G) and it is possible that a similar radical (a_N = 12.1 and a_H = 1.35 G) was formed during the early part of this experiment. However, it did not persist, nor intensify on further addition of peroxide. The most intriguing aspect of these results is the relative unreactivity of both ' reactive ' centres in the nitrone-nitroxide (13) to benzoyloxy (and phenyl) radicals. Significantly, decomposition of the phenyl radical-source phenyl azotriphenylmethane in a solution of the nitrone-nitroxide in benzene also caused only a slight decrease in the intensity of the observed spectrum.

(c) *Di-t-butyl peroxide and di-t-butyl peroxalate.* When di-t-butyl peroxalate was added to a solution of the nitrone-nitroxide (13; R = Bu^t) at room temperature the original e.s.r. spectrum rapidly diminished and was replaced by a weak triplet of doublets (a_N = 12.8 and a_H = 1.6 G) and a triplet (a_N = 9.3 G). Similar addition to an equimolar mixture of phenyl t-butyl nitrone and the nitrone-nitroxide (13; R = Bu^t) also caused rapid disappearance of the original spectrum and formation of a triplet of doublets (a_N = 13.9, a_H = 1.9 G), very similar to that formed when di-t-butyl peroxalate was added to phenyl t-butyl nitrone alone. Irradiation of a solution of the nitrone-nitroxide in carbon tetrachloride and di-t-butyl peroxide (1 : 1) at 0 to −20 °C resulted in slow loss of the initial e.s.r. spectrum. A residual very weak triplet of doublets (a_N = 14.0, a_H = 1.8 G) was barely detectable.

t-Butoxyl radicals usually couple O (of Bu^{t}O·) to *para*-C with aryl nitroxides and presumably a similar process is occurring here. Since there is no indication of diradical formation it would appear that this precedes addition of t-butoxyl to the nitrone function of (13; R = Bu^t). The weak triplet of doublets indicates formation of a t-alkyl secondary alkyl nitroxide [perhaps (24)] from which an acyl nitroxide[3] (a_N = 8.3 G) (25?) would ultimately arise.

Our conclusion is that the nitrone function of (13; R = Bu^t) is much less reactive than that of t-butyl phenyl nitrone towards radicals, and hence (11) is not a useful source of bisnitroxides. Anionic addition to the nitrone group of (13; R = Bu^t) has still to be investigated.

EXPERIMENTAL

I.r. spectra were measured as Nujol mulls and n.m.r. spectra in deuteriochloroform unless stated otherwise. Petrol refers to light petroleum, b.p. 60—80 °C. Merck silica gel GF_{254} or HF_{254} was used for chromatographic separations.

N-*t-Butyl*-N-(p-*methoxymethylphenyl*)*hydroxylamine.* —To the Grignard reagent prepared from *p*-methoxymethylbromobenzene [18] (10 g, 0.05 mol) and magnesium (2.4 g) in ether–tetrahydrofuran (THF) (1 : 1) (100 ml), 2-methyl-2-nitrosopropane [19] (4 g, 0.046 mol) in ether (80 ml) was added dropwise with stirring under nitrogen. Stirring was continued for 30 min before water was added. The ethereal layer was separated and the aqueous layer was extracted with several portions of ether. The dried ($MgSO_4$) ethereal extracts were evaporated and the residue was crystallised from hexane to give N-*t-butyl*-N-(p-*methoxymethylphenyl*)-*hydroxylamine* (5.9 g, 57%), m.p. 97—98 °C as needles (Found: C, 69.2; H, 8.8; N, 6.8. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.1; N, 6.7%); $\lambda_{max.}$ (EtOH) 252 (log ε 3.75); $\nu_{max.}$ 3 300—3 100 cm^{-1}; δ 1.05 (9 H, s, t-Bu), 3.35 (3 H, s, Me), 4.38 (2 H, s, CH_2) 1.18 (4 H, s, Ar-H), and 7.3—7.5 (1 H, br s, OH).

N-*t-Butyl*-N-(p-*formylphenyl*)*hydroxylamine.*—*Method* (*i*). *N*-t-Butyl-*N*-(*p*-methoxymethylphenyl)hydroxylamine (3 g, 0.014 mol) in benzene (50 ml) was shaken with silver oxide (3.5 g) and magnesium sulphate (5 g) until oxidation was complete (t.l.c.). The reaction mixture was filtered and the filtrate was concentrated (to *ca.* 10 ml) and left for *ca.* 14 days. The solution was diluted with benzene and then shaken with 2M hydrochloric acid (100 ml) for 8 h. The organic phase was separated and extracted with several portions of 2M hydrochloric acid. The combined acidic extracts were made alkaline and the resulting precipitate extracted into dichloromethane. The dried extracts were evaporated and the residue was chromatographed (preparative t.l.c.) using chloroform as eluant to give (*a*) a red nitroxide fraction which was not investigated; (*b*) *N*-t-butyl-*N*-(*p*-formylphenyl)hydroxylamine (0.96 g, 69%), m.p. 89—90 °C (from hexane) (Found: C, 68.1; H, 7.5; N, 7.6. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.8; N, 7.3%); $\nu_{max.}$ 3 240—3 180 and 1 695 cm^{-1}; δ 1.16 (9 H, s, t-Bu), 6.52 (1 H, br s, OH), 7.34—7.81 (4 H, m, Ar-H), and 9.92 (1 H, s, CHO).

Method (*ii*). To the Grignard reagent prepared from 2-(*p*-bromophenyl)-1,3-dioxolan [20] (26.13 g, 0.11 mol) in ether–THF (2 : 1) (150 ml), 2-methyl-2-nitrosopropane (9.9 g, 0.11 mol) in ether (180 ml) was added dropwise with stirring under nitrogen. Water was then added and the ethereal phase was separated and the aqueous phase was extracted with ether. The combined, dried, ethereal extracts were evaporated and the residue was hydrolysed as in method (i). Chromatography (preparative t.l.c.) of the hydrolysate with chloroform gave the *hydroxylamine* (8.4 g, 38%).

Derivatives of N-*t-butyl*-N-(p-*formylphenyl*)*hydroxylamine.* —(i) *The oxime.* Treatment of the aldehyde (50 mg) with hydroxylamine hydrochloride (23 mg) and triethylamine (65 mg) in ethanol under reflux for 1 h gave N-*t-butyl*-N-(p-*hydroxyiminoformylphenyl*)*hydroxylamine* (37 mg, 69%) as needles, m.p. 156—158 °C (from chloroform–petrol) (Found: C, 63.6; H, 7.7; N, 13.4%; M^+, 208.121 4. $C_{11}H_{16}N_2O_2$ requires C, 63.4; H, 7.7; N, 13.5%; *M*, 208.121 1); $\nu_{max.}$ (KBr) 3 450 and 3 300—3 200 cm^{-1}; δ (CD_3OD) 1.13 (9 H, s, t-Bu), 7.2—7.5 (4 H, m, Ar-H), and 8.01 (1 H, s, CH=N); *m/e* 208 (6%) (M^+), 152 (100), and 135 (32).

(ii) *The hydrazone*. Treatment of the aldehyde (98 mg, 0.51 mmol) with 98% hydrazine hydrate (30 mg, 0.94 mmol) in ethanol at room temperature for 8 h gave N-*t-butyl*-N-(p-*hydrazonoformylphenyl*)*hydroxylamine* (92 mg, 87%) as pale yellow needles, m.p. 196—197 °C (from chloroform–petrol) (Found: C, 63.6; H, 8.0; N, 20.2%; M^+, 207.137 1. $C_{11}H_{17}N_3O$ requires C, 63.7; H, 8.3; N, 20.2%; *M*, 207.137 1); $\nu_{max.}$ 3 240—3 200 cm^{-1}; δ ([$^2H_6$]DMSO) (two isomers) 1.07 and 1.12 (each 9 H, s, t-Bu), 7.11—7.80 (4 H, m, Ar-H), *ca.* 8.26 (2 H, br s, NH_2), 8.45 (1 H, br s, OH), and 8.63 (1 H, s, CH=N); *m/e* 207 (M^+) (10%), 191 (5), 176 (6), 167 (18), 160 (4), 151 (100), 134 (94), and 83 (25).

(iii) *Imines*. Treatment of the aldehyde (99 mg, 0.52 mmol) with t-butylamine (57 mg, 78 mmol) in ethanol (5 ml) overnight at room temperature gave N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*]-*t-butylamine* (69 mg, 54%), as needles, m.p. 147—149 °C (from petrol) (Found: C, 72.5; H, 9.8; N, 11.6%; M^+, 248.188 4. $C_{15}H_{24}N_2O$ requires C, 72.5; H, 9.7; N, 11.3%; *M*, 248.188 8); $\nu_{max.}$ 3 220—3 160 cm^{-1}; δ 1.10 (9 H, s, *Bu*^{t}NOH), 1.18 (9 H, s, *Bu*^{t}N=), 7.24—7.68 (4 H, q, Ar-H), 8.24 (1 H, s, CH=N); *m/e* 248 (9%) (M^+), 217 (9), 201 (7). 192 (45), 177 (100), 161 (9), and 136 (84). Similarly prepared were N-[p-(N′-*t-butylhydroxylamino*)-*benzylidene*]*aniline* (58%), needles, m.p. 168—169 °C (from ethanol) (Found: C, 76.4; H, 7.5; N, 10.3%; M^+, 268.157 8. $C_{17}H_{20}N_2O$ requires C, 76.1; H, 7.5; N, 10.4%; *M*, 268.157 5); $\nu_{max.}$ 3 200—3 170 cm^{-1}; δ 1.14 (9 H, s, t-Bu), 6.26 (1 H, br s, OH), 7.22—7.81 (9 H, m, Ar-H), and 8.38 (1 H, s, CH=N); *m/e* 268 (3.5%) (M^+), 252 (6), 237 (9), 212 (100), and 195 (32); N-[p-(N′-*t-butylhydroxylamino*)-*benzylidene*]-p-*butylaniline* (81%), m.p. 131—134 °C (from benzene–petrol) (Found: C, 77.7; H, 8.5; N, 8.8%; M^+, 324.220 0. $C_{21}H_{28}N_2O$ requires C, 77.7; H, 8.7; N, 8.6%; *M*, 324.220 2); $\nu_{max.}$ (KBr) 3 220–3 140 cm^{-1}; δ 1.15 (9 H, s, t-Bu), 1.88—2.25 (9 H, m, Bu), 6.7 (1 H, br s, OH), 7.25—7.8 (4 H, m, ArH), and 8.4 (1 H, s, CH=N); *m/e* 324 (9%) (M^+), 308 (18), 293 (16), 268 (100), 252 (6), 225 (13), and 209 (18); N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*]-p-*hydroxyaniline* (50%) as needles, m.p. 229—230 °C (from ethanol–petrol) (Found: C, 71.9; H, 7.3; N, 10.1%; M^+, 284.152 5. $C_{17}H_{20}N_2O_2$ requires C, 71.8; H, 7.1; N, 9.9%; *M*, 284.152 4); $\nu_{max.}$ 3 220—3 050 cm^{-1}; δ ([$^2H_6$]DMSO) 1.05 (9 H, s, t-Bu), 6.8—7.26 (4 H, m, Ar-H), 7.2—7.6 (4 H, q, Ar-H) 8.37 (1 H, br s, OH), 8.46 (1 H, s, CH=N), and 9.36 (1 H, br s, OH); *m/e* 284 (M^+) (9%), 268 (7), 253 (7), 228 (100), and 211 (45); and *ethyl* N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*-D-(−)-α-*phenylglycinate* (47%), needles, m.p. 127—129 °C (from carbon tetrachloride–petrol) (Found: C, 71.1; H, 7.2; N, 7.8%; M^+, 354.193 9. $C_{21}H_{26}N_2O_3$ requires C, 71.2; H, 7.4; N, 7.9%; *M*, 354.194 3); $\nu_{max.}$ 3 180—3 100 and 1 745 cm^{-1}; δ 1.1 (9 H, s, t-Bu), 1.23 (3 H, t, Me), 4.21 (2 H, q, CH_2), 5.15 (1 H, s, CH), 6.52 (1 H, br s, OH), 7.22—7.75 (4 H, m, Ar-H), and 8.27 (1 H, s, CH=N); *m/e* 354 (5%) (M^+), 338 (5), 298 (20), 265 (79), 250 (25), 225 (100), and 209 (28).

(iv) *Nitrones*. Treatment of the aldehyde (404 mg, 2.09 mmol) with *N*-t-butylhydroxylamine (312 mg, 3.5 mmol) in ethanol at room temperature gave N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*]-*t-butylamine* N-*oxide* (330 mg, 60%), m.p. 199.5—200.5 °C (from chloroform–petrol) (Found: C, 67.6; H, 9.3; N, 10.9%; M^+, 264.183 8. $C_{15}H_{24}N_2O_2$ requires C, 68.1; H, 9.2; N, 10.6%; *M*, 264.183 7); $\nu_{max.}$ 3 240—3 120, 1 601, and 1 200 cm^{-1}; δ 1.09 (9 H, s, *t-Bu*–NOH), 1.58 [9 H, s, *t-Bu*–$\overset{+}{N}(\bar{O})$=], 6.48 (1 H, s, CH=N), 7.48 (1 H, br s, OH), and 7.24—8.42 (4 H, m, Ar-H); *m/e* 264 (9%) (M^+), 208 (16), 177 (5.5), 152 (100), and 135 (18). Similarly prepared was N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*]*aniline* N-*oxide* (78%), as needles, m.p. 167.5—169.5 °C (from benzene) (Found: C, 71.8; H, 7.1; N, 9.7%; M^+, 294.152 4. $C_{17}H_{20}N_2O_2$ requires C, 71.8; H, 7.1; N, 9.9%; *M*, 284.152 4); $\nu_{max.}$ 3 100—3 020, 1 600, and 1 210 cm^{-1}; δ 1.15 (9 H, s, t-Bu), 6.24 (1 H, br s, OH), 7.86 (1 H, s, CH=N), and 7.36—8.31 (9 H, m, Ar-H); *m/e* 284 (M^+) (22%), 268 (14), 252 (6), 237 (7), 228 (100), 211 (50), and 195 (16).

(v) N-*t-Butyl*-N-(p-*hydroxymethylphenyl*)*hydroxylamine*. The aldehyde (129 mg) in ethanol (8 ml) was shaken with platinum oxide under hydrogen. The catalyst was collected and the filtrate was evaporated. Chromatography of the residue using chloroform as eluant gave the *product* (67 mg, 51%), m.p. 125.5—128.5 °C (from benzene) (Found: C, 67.7; H, 8.6; N, 7.5%; M^+, 195.125 8. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%; *M*, 195.125 9); $\nu_{max.}$ 3 240—3 140 cm^{-1}; δ 1.13 (9 H, s, t-Bu), 4.64 (2 H, s, CH_2), 7.19 (4 H, s, Ar-H), and 7.26 (2 H, s, 2 OH); *m/e* 195 (M^+) (3%), 179 (4.5), 164 (28), 148 (23), 139 (100), and 122 (28).

(vi) p-(N-*t-Butylhydroxylamino*)*benzyl* 3′,5′-*di-t-butyl*-4′-*hydroxybenzoate*. A solution of *N*-t-butyl-*N*-*p*-hydroxymethylphenylhydroxylamine (200 mg, 1.02 mmol) and triethylamine (144 mg, 1.43 mmol) in benzene–ether (1 : 1) (10 ml) was added to 3,5-di-t-butyl-4-hydroxybenzoyl chloride (385 mg, 1.43 mmol) in benzene (10 ml) and the mixture stirred for 24 h. After removal of triethylamine hydrochloride the filtrate was washed with saturated sodium hydrogencarbonate solution and then dried ($MgSO_4$). Chromatography of the residue, after removal of solvent, using chloroform as eluant, gave the *product* (40 mg, 9%), m.p. 130 °C (from carbon tetrachloride–petrol) (Found: M^+, 427.272 4. $C_{26}H_{37}NO_4$ requires *M*, 427.272 2); $\nu_{max.}$ 3 622 (Ar-OH), 3 250—3 050 (NOH), and 1 712 cm^{-1}; δ 1.13 (9 H, s, t-Bu), 1.44 (18 H, s, 2 t-Bu), 5.31 (2 H, s, CH_2), 5.66 (1 H, br s, NOH), 7.2—7.3 (4 H, m, Ar-H), and 7.93 (2 H, s, Ar-H); *m/e* 427 (M^+) (1%), 411 (40), 396 (56), 370 (4), and 235 (100).

(vii) 3-[p-(N′-*t-Butylhydroxylamino*)*phenyl*]-2,5-*diphenyloxazolidine*. A solution of *N*-[*p*-(*N*′-t-butylhydroxylamino)-benzylidene]aniline *N*-oxide (110 mg, 0.39 mmol) and styrene (209 mg, 2.61 mmol) in toluene (10 ml) was heated at 100—110 °C for 10 h. The solid, which separated on cooling, was collected, washed with petrol, and crystallised from benzene–petrol to give *the product* (59 mg, 39%), m.p. 172—174 °C (Found: C, 77.2; H, 7.2; N, 7.5%; M^+, 388.215 4. $C_{25}H_{28}N_2O_2$ requires C, 77.3; H, 7.3; N, 7.2%; *M*, 388.215 0); $\nu_{max.}$ 3 180—3 120 cm^{-1}; δ 1.12 (9 H, s, t-Bu), 2.3—2.6 (1 H, m, C*H*H), 3.0—3.28 (1 H, m, CH*H*), 4.81—4.96 (1 H, t, CHN), 5.08—5.25 (1 H, q, C*H*Ph), and 6.9—7.49 (14 H, m, Ar-H); *m/e* 388 (M^+) (28%), 372 (3), 331 (5), 280 (6), 264 (20), and 224 (100).

Preparation of Di- and Tri-hydroxylamines.*—(i) *Bis*-{N-[p-(N′-*t-butylhydroxylamino*)*benzylidene*]}-m-*phenylenediamine*. A solution of *N*-t-butyl-*N*-(*p*-formylphenyl)-hydroxylamine (101 mg, 0.52 mmol) and *m*-phenylenediamine (28 mg, 0.26 mmol) was left for 21 h. The precipitate which separated was collected and washed with hot chloroform and ethanol to give the *dihydroxylamine* (100 mg, 83%), m.p. 206—207 °C (Found: M^+, 458.268 5. $C_{28}H_{34}N_4O_2$ requires *M*, 458.268 1); $\nu_{max.}$ 3 220—3 160 cm^{-1};

*A suitable crystallising solvent could not be found for these insoluble dihydroxylamines, hence the absence of satisfactory carbon and hydrogen analyses.

δ (CF_3CO_2D) 1.62 (18 H, s, t-Bu), 4.10 (2 H, s, C CH=N), 7.82 (4 H, s, Ar-H), and 7.92—8.33 (8 H, m, Ar-H); *m/e* 458 (M^+) (3%), 442 (9), 426 (100), 411 (56), 385 (28), 370 (10), 355 (79), and 314 (28).

(ii) *Bis-*{N-[p-(N'-*t-butylhydroxylamino*)*benzylidene*]}-p-*phenylenediamine*. This was prepared from *p*-phenylenediamine (28 mg, 0.26 mmol) and *N*-t-butyl-*N*-(*p*-formylphenyl)-hydroxylamine (102 mg, 0.52 mmol) as described in (i). The product (111 mg, 92%) had m.p. 224—227 °C (Found: M^+, 458.268 5. $C_{28}H_{34}N_4O_2$ requires *M*, 458.268 1); $\nu_{max.}$ 3 140—3 080 cm^{-1}; δ (CF_3CO_2D) 1.60 (18 H, s, t-Bu), 4.08 (2 H, s, 2 × CH=N), 7.79 (4 H, s, Ar-H), 7.90—8.31 (8 H, m, Ar-H); *m/e* 458 (M^+) (11%), 442 (11), 427 (100), 411 (7), 385 (25), 370 (16), 355 (22), 345 (50), 329 (9), and 314 (22).

(iii) 1,3-*Dihydroxy*-2-[p-(N-*t-butylhydroxylamino*)*phenyl*]-4,4,5,5-*tetramethyl*-2-*imidazoline*. A solution of *N*-t-butyl-*N*-(*p*-formylphenyl)hydroxylamine (150 mg, 0.78 mmol) and 2,3-bis(hydroxylamino)-2,3-dimethylbutane sulphate (255 mg, 0.78 mmol) in ethanol was refluxed with sodium carbonate (124 mg) for 18 h. The reaction mixture was cooled and the precipitate which separated was collected and washed with ethanol and water to give the *trihydroxylamine* (96 mg, 38%), m.p. 193—195 °C (Found: M^+, 323.220 6. $C_{17}H_{29}N_3O_3$ requires *M*, 323.220 8); $\nu_{max.}$ 3 220—3 150 cm^{-1}; δ ([$^2H_6$]DMSO) 1.93 (9 H, s, t-Bu), 3.31 (12 H, s, 4 Me), 4.47 (1 H, s, CH), 7.08—7.38 (4 H, m, Ar-H), 7.68 (2 H, s, 2 × OH), and 8.18 (1 H, br s, OH); *m/e* 323 (M^+ (0.4%), 305 (2), 249 (7), 233 (45), 217 (18), 177 (100), 159 (25), and 152 (32).

Preparation of Mono- and Bis-nitroxides.—The nitroxides were prepared by stirring or shaking the corresponding hydroxylamines (0.01 mol) with silver(I) oxide (0.0075 mol) and magnesium sulphate in carbon tetrachloride for 1—2 h until no hydroxylamine could be detected. The reaction mixture was then filtered and the filtrate was evaporated. The residue was chromatographed using chloroform as eluant.

N-*t-Butyl* N-[p-(N'-*t-butylformimidoyl*)*phenyl*] *nitroxide* N'-*oxide* (90%) formed green rods, m.p. 114—115 °C (from petrol) (Found: C, 68.3; H, 9.1; N, 10.8%; M^+, 263.175 6. $C_{15}H_{23}N_2O_2$ requires C, 68.4; H, 8.8; N, 10.6%; *M*, 263.175 9); $\lambda_{max.}$ (log ε) 210 (3.85), 223 (3.81), 260 (3.86), 352 (4.25sh), and 362 (4.29) nm; $\nu_{max.}$ (KBr) 1 350 and 1 180 cm^{-1}; *m/e* 263 (3%) (M^+), 248 (7), 207 (19), 151 (100), and 136 (20).

N-*t-Butyl* N-[p-(N'-*phenylformimidoyl*)*phenyl*] *nitroxide* N'-*oxide* (69%) gave dark green rods, m.p. 104.5—106 °C (from benzene–petrol) (Found: C, 71.8; H, 6.7; N, 9.7%; M^+, 283.144 2. $C_{17}H_{19}N_2O_2$ requires C, 72.1; H, 6.8; N, 9.9%; *M*, 283.144 6); $\lambda_{max.}$ (log ε) 207 (4.00), 228 (3.91), 264 (3.75), and 380 (4.29) nm; $\nu_{max.}$ 1 345 and 1 190 cm^{-1}; *m/e* 283 (0.4%) (M^+), 268 (9), 252 (10), 237 (11), 227 (18), 211 (7), 177 (40), and 162 (100).

2-(p-*t-Butylamino*-N-*oxyl*)*phenyl*-4,4,5,5-*tetramethylimidazoline*-1-*oxyl* 3-*oxide* was chromatographed on Kieselgel 60F254 to give purple rods, m.p. 163 °C (from carbon tetrachloride–petrol) (Found: C, 63.7; H. 8.0; N, 12.3%; M^+, 319.189 4. $C_{17}H_{25}N_3O_3$ requires C, 63.9; H, 7.9; N, 13.2%; *M*, 319.189 4); $\lambda_{max.}$ (log ε) 212 (2.6), 235 (2.51), and 350 (4.2) (2.5%), 304 (2), 263 (100), 174 (6), and 159 (5).

E.S.R. Measurements.—These were made on a Varian 104A spectrometer. All solutions were degassed either by freeze-thaw cycles or by nitrogen bubbling.

We thank the S.R.C. for grants to (J. H. and S. P. H.) and for an equipment grant.

[0/900 *Received*, 12*th June*, 1980]

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