Further Nitroxide-producing Reactions of Aromatic *C*-Nitroso-compounds in Benzene Solution

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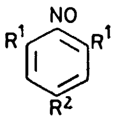
E.s.r. studies show that nitrosobenzene and 2,4,6-trichloronitrosobenzene react slowly in benzene solution under nitrogen with many carbonyl compounds to give moderately stable nitroxides formed by additions to their enolic tautomers. The formation of nitroxides from diethyl and di-isopropyl ketones may involve a further molecular rearrangement. Short lived arylnitroxides ArNHO· are probably formed also and sometimes can be detected as transient initial products of reactions between nitroso-compounds and arylhydroxylamines, hydrazobenzene, thiols, and a few phenols. Thiophenols react with these nitroso-compounds to give thionitroxide radicals ArN(O·)SAr′, but alkylated phenols yield first the corresponding aryloxyl radicals and then either benzylic or nuclear-substituted nitroxides, depending on the structures of their substituent groups.

The hyperfine splitting constants of the new nitroxide radicals observed in this study are tabulated. The work illustrates the general tendency of aromatic *C*-nitroso-compounds to exhibit free radical reactivity in a non-ionizing solvent.

It has recently been found that mixtures, in benzene under nitrogen, of aromatic *C*-nitroso-compounds and olefins having a wide range of substituents exhibit the e.s.r. spectra of nitroxide free radicals which show that the two reactants combine by way of one-electron transfer from C=C to N=O bonds.[1] Exploratory studies using the same experimental technique have now shown that organic compounds of certain other structural types react with nitroso-compounds in benzene to give similar nitroxide free radicals.

(A) *Reactions of Enolizable Compounds.* When studying the additions of 2,4,6-trichloronitrosobenzene (1) to unsaturated compounds, mesityl oxide ($\mathrm{Me_2C{:}CH{\cdot}COMe}$) was examined in the expectation that it would give a 6-lined e.s.r. spectrum indicative of the addition of the nitroso group to the less-substituted end of its double bond. Surprisingly there resulted a well defined e.s.r. spectrum of the type of Figure 1, with nine main lines indicative of a nitroxide of structure $\mathrm{ArN(O{\cdot})CH_2R}$. This spectrum can eventuate however from the addition of (1) to the enolic form of mesityl oxide, *i.e.* $\mathrm{Me_2C{:}C(OH){:}CH_2}$, a trace of which might be present and could be formed tautomerically in the unsaturated ketone. In confirmation of this interpretation it was then found that benzene solutions of acetone and (1) slowly give a similar spectrum which persists for several hours. Further testing then showed that several other enolizable ketones and aldehydes also give with (1) well defined nitroxide spectra which are listed in Table 1. All have $g = 2.006\,25$.

Nitrosobenzene (2) and *p*-chloronitrosobenzene (3) also developed persisting e.s.r. spectra with easily enolizable compounds such as acetone, cyclohexanone, and acetylacetone but the spectra were not sufficiently well resolved for full analysis. The initial signals from acetone, acetylacetone, and di-isopropyl ketone with (2) closely resembled that of the phenylnitroxide radical, PhNHO·. From each compound tested the later signals with (2) or (3) comprised three partly overlapping groups of lines *ca.* 1.05—1.1 mT apart.

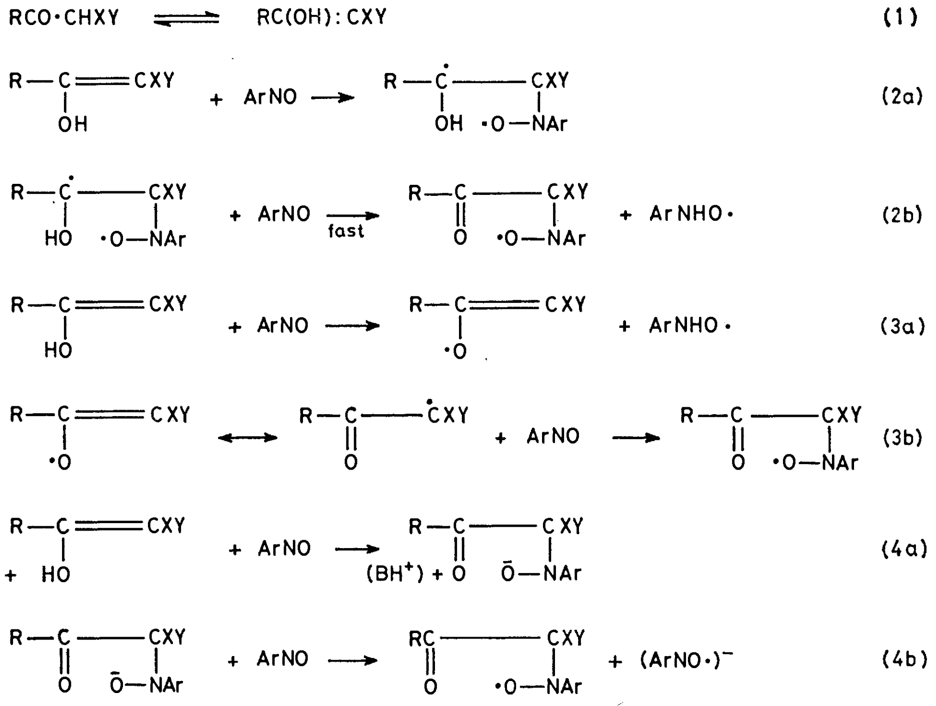


(1) $R^1 = R^2 = Cl$
(2) $R^1 = R^2 = H$
(3) $R^1 = H$, $R^2 = Cl$

In contrast to the olefins which with (1) gave distinct e.s.r. signals after a few minutes the carbonyl compounds of Table 1, though used in very large excess [2—3 ml in 10 ml of benzene and 5—10 mg of (1)], develop their spectra slowly; they are usually recognizable after 20—30 min, strengthen progressively for at least an hour, and persist for several hours or days in stored solution under nitrogen but gradually become diffuse. Good, well resolved signals are most rapidly obtainable from liquid carbonyl compounds which already contain detectable percentages of enols or have fairly high enolization rates.[2] With other compounds such as acetaldehyde, isobutyraldehyde, or ethyl phenylacetate the blue colour of (1) or (2) persists for several hours; these all gave weak spectra identifiable with less certainty, those remaining after a day of storage possibly being due to secondary reactions. Thus from acetaldehyde and (1) the persisting weak signal had six diffuse lines and could possibly come from aldol, whilst simple nitroparaffins did not give identifiable signals.

Reaction Mechanism.—The qualitative evidence presented above indicates that nitroxide radical formation from enolizable carbonyl compounds follows an initial tautomerism (equation 1) which since these compounds have been used in concentrated solution in benzene (see above) could be intermolecularly catalysed. Again, as from olefins,[1] the persisting signals must be those of mono-radicals and hence an oxidative step is involved, as in reactions (2)—(4), though with the nitroso-compound (1) this has not been noticed. Scheme 1 gives probable routes for the formation of nitroxides having the e.s.r. spectra listed in Table 1.

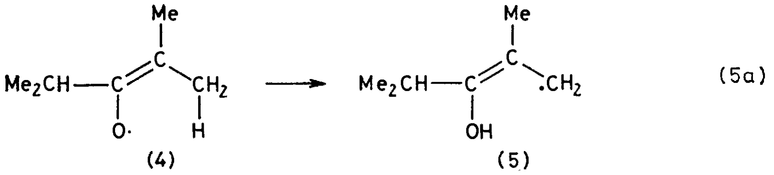
Reaction (4) is a heterolytic base-catalysed addition followed by the well established one-electron oxidation of a hydroxylamine by a nitroso-compound.[3] The others are free-radical reactions, reaction (2) following the route suggested for the addition of nitroso-compounds to olefins and reaction (3) recognizing the fact that enols easily react with several mild one-electron oxidizing agents.[4] Reaction (3) could alternatively be formulated in terms of electron transfer and not hydrogen transfer, though radical-ion formation is not a favoured type of reaction in benzene.



SCHEME 1

Further experimental work will be required to discriminate between these mechanisms. Base catalysis, essential for reaction (4), should hasten nitroxide formation by all three suggested routes since it invariably accelerates the tautomerism (1). Unfortunately bases, including tertiary amines soluble in benzene, react rapidly with (1) to give yellow solutions which contain chloride anions and give complicated e.s.r. spectra which have not been identified; e.s.r. spectra can also be observed after admixture of (2) with bases under nitrogen. In view of these findings it is not surprising that nitroxide spectra have not been detected in mixtures of (1) with compounds such as 2,4-dinitrotoluene or *p*-nitrobenzyl cyanide which are known to require base catalysis for condensation with *p*-nitrosodimethylaniline.

Anomalous Spectra.—(a) Di-isopropyl ketone soon gives with (1) the well resolved e.s.r. spectrum shown in Figure 1. This cannot be that of a direct adduct of its enol $Me_2CH\cdot C(OH)\colon CMe_2$ but could be formed from it by way of an intramolecular rearrangement to (5) of the enolic radical (4) obtained from di-isopropyl ketone by one-electron oxidation as in equation 3(a) and illustrated by equation (5).



$$Me_2CH\cdot C(OH)\colon CMe\cdot CH_2\cdot\ +\ ArNO \longrightarrow Me_2CH\cdot C(OH)\colon CMe\cdot CH_2\cdot N(O\cdot)Ar \quad (5b)$$

The mechanism of reaction (5) is similar to that suggested for the formation of benzylic nitroxides from (1) and 2,4,6-trimethyl- or 2-methyl-4,6-di-t-butylphenol (see Scheme 2 later).

Concentrated solutions (3 ml in 10 ml benzene) of diethyl ketone give with (1) a mixed spectrum showing nine lines corresponding to Figure 1 together with a 6-lined spectrum as expected for the enol $EtC(OH)\colon CHMe$, but with more dilute solutions only the 6-lined spectrum was observed and on storage of reaction mixtures this was the more persistent spectrum. Ethyl methyl ketone which reacted very slowly with (1) gave only a 6-lined spectrum and isopropyl methyl ketone gave a definite 3-lined spectrum only after long storage. No anomalies were observed with either cyclopentanone or cyclohexanone, with which a rearrangement similar to that of equation (5) is spatially impossible.

TABLE 1

E.s.r. spectra from 2,4,6-trichloronitrosobenzene and carbonyl compounds R^1–CO–R^2 (splittings in mT ±0.005)

R^1	R^2	a_N	a_{CH_2}	a_{CH}
Me	Me	1.30	0.91	
Me	Pr^i	1.22		
Me	Bu^t	1.24	0.81	
Me	$CH{:}CMe_2$	1.26	0.87	
Me	$CH{:}CH_2$	1.25	0.82	
Me	$C(OH)Me_2$ w	1.25	0.88	
Me	Ph	1.27		0.60
Me	p-$Me{\cdot}C_6H_4$	1.25	0.77	
Me	Et	1.25		0.50
Et	Et (dilute)	1.25		0.51
Et	Et (conc.)	1.24	0.82	
Pr^i	Pr^i	1.22	0.84	
H	Me w ?($MeCH(OH){\cdot}CH_2$)	1.28		0.47

R^1	R^2	a_N	a_{CH}
$PhCH_2$	$PhCH_2$	1.27	0.54
Cyclopentanone		1.30	0.30
Cyclohexanone		1.26	0.50_5
Me	$CH_2{\cdot}COMe$	1.20_5	0.52
Me	$CH_2{\cdot}CO_2Et$	1.18	0.50
Me	$CHMe{\cdot}CO_2Et$	1.16	
EtO	$CH_2{\cdot}CO_2Et$	1.25	0.49
EtO	CH_2Ph w	1.25	0.57
H	Et	1.26	0.31
H	Pr^n	1.27	0.37
H	Pr^i	1.21	
H	C_6H_{13}	1.26	0.34

w = very weak spectra.

(b) Acetophenone in both concentrated or dilute solutions reacted quickly with (1) to give a 6-lined spectrum having a_N 1.27, a_{CH} 0.60 mT but p-methylacetophenone gave the expected 9-lined spectrum (see Table 1). Possibly the radical from acetophenone results from a secondary enolization (6).

$$PhCO{\cdot}CH_2{\cdot}N(O{\cdot})Ar \longrightarrow PhC(OH){:}CH{\cdot}N(O{\cdot})Ar \quad (6)$$

Tests with several less easily available ketones are evidently needed to rationalize fully all these experimental observations.

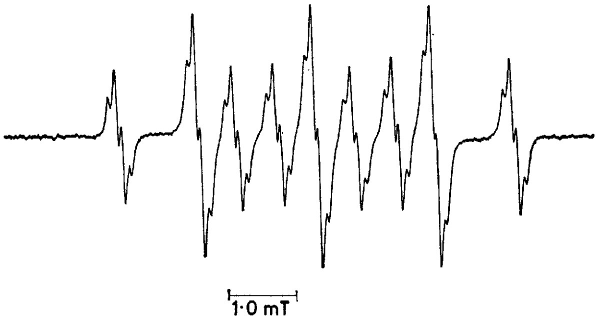


FIGURE 1 E.s.r. spectrum from 2,4,6-trichloronitrosobenzene and di-isopropyl ketone. This is typical of nitroxides of the type $C_6H_2Cl_3$–N(O•)–CH_2R

(B) *Reactions of Hydroxylamines, Thiols, and Phenols.* The e.s.r. spectrum of the 2,4,6-trichlorophenyl nitroxide radical, $C_6H_2Cl_3NHO{\cdot}$, has not been detected unequivocally from reactions of (1) with olefins, including enols. Attempts to detect this radical by effecting the reduction of (1) by homolytic hydrogen transfer [reaction (7)] in benzene have led to the detection of further new radicals.

$$ArNO + HR \longrightarrow ArNHO{\cdot} + R{\cdot} \quad (7)$$

(i) *Hydroxylamines.*—Reactions (8) between nitroso-compounds and hydroxylamines rapidly generate primary nitroxide radicals[3] which then dimerise to azoxy-compounds, the composition of the pseudo-equilibrated mixtures depending on the redox potentials of the participating molecules.

$$Ar^1NO + Ar^2NHOH \rightleftharpoons Ar^1NHO{\cdot} + Ar^2NHO{\cdot} \rightleftharpoons Ar^1NHOH + Ar^2NO \quad (8)$$

When (1) in benzene is mixed with a similar or larger concentration of N-phenylhydroxylamine the only e.s.r. spectrum to be detected under nitrogen is that of the phenylnitroxide radical, $PhNHO{\cdot}$ (a_N 0.97, a_{NH} 1.25, $a_{H_{o,p}}$ 0.3, a_{H_m} 0.1 mT) and similarly with N-p-chlorophenylhydroxylamine only the radical p-$ClC_6H_4{\cdot}NHO{\cdot}$ was detected (a_N 0.94, a_{NH} 1.23, a_{H_o} 0.30, a_{H_m} 0.1 mT). These splitting constants are *ca.* 7% less than those measured in methanol and *ca.* 10% less than values reported earlier in aqueous alcohols. However when warm (40—50 °C) saturated solutions of (1) are mixed with very dilute benzene solutions of either of these hydroxylamines then initially weak spectra showing six broad lines are produced. These have a_N 0.82, a_{NH} 1.14 (±0.01) mT, and g 2.006 25 as expected for $C_6H_2Cl_3{\cdot}NHO{\cdot}$ and consistent with the values a_N 0.92 and a_{H_m} 0.13 published some years ago[5] for the corresponding radical-anion, $(C_6H_2Cl_3{\cdot}NO{\cdot})^-$, in 80—90% methanol. A stronger and much clearer e.s.r. spectrum, with the same splitting constants, has been obtained by the reduction in benzene of (1) by hydrazobenzene.

(i) *Thiols.*—Nitrosobenzene (2) in benzene when treated with a small amount of β-mercaptoethanol gave immediately the e.s.r. signal of the $PhNHO{\cdot}$ radical (a_N 0.97, a_{NH} 1.26, $a_{H_{o,p}}$ 0.31, a_{H_m} 0.1 mT) which slowly decayed. With thioglycollic acid (*ca.* 2 ml in 10 ml benzene) the same signal was formed but with larger splitting constants (a_N 1.04, a_{NH} 1.30, $a_{H_{o,p}}$ 0.33, a_{H_m} 0.1 mT). Compound (1) with a small amount of β-mercaptoethanol, however, gave a 3-lined spectrum with a_N 1.45 mT, but with larger amounts of the thiol broad inner lines developed having a_N *ca.* 0.87, a_{NH} 1.22 mT ±0.03, probably the spectrum of the $C_6H_2Cl_3NHO{\cdot}$ radical. With thioglycollic acid, however, the weak e.s.r. spectra had only six overlapping lines with a_N 0.9, a_{NH} 1.2 mT ± 0.05 and $g = 2.0063$ and the benzene solutions took hours to change from blue through green to yellow even with the thiol present in very large excess. These enhanced splitting constants may exemplify the polar effect of the large percentages of thiol used (see above).

Thiophenols, however, gave quite different, strong, well resolved spectra with both (1) and (2) (Table 2). They reached their maximum intensity in *ca.* 10 min, were evidently weaker in an hour, and had disappeared almost completely in *ca.* 2 h from the time of admixture. From their splitting constants and higher g values they

TABLE 2

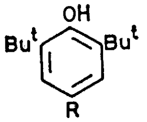
Thionitroxide radicals from thiophenols

Reactants		Splitting constants (mT) ±0.005			
		a_N	$a_{H_{o,p}}$	a_{H_m}	g
PhSH	PhNO	1.16	0.265	0.09	2.0058
PhSH	$C_6H_2Cl_3NO$	1.40		0.07	2.0066
p-MeC_6H_4·SH	PhNO	1.18	0.260	0.09	2.0058
p-MeC_6H_4·SH	$C_6H_2Cl_3NO$	1.42		0.07	2.0066

are undoubtedly thionitroxide radicals of structure $Ar^1N(O\cdot)-SAr^2$, formed by reactions (7) and (9); these radicals are known to have low thermal stability.[6] The 3-lined spectrum obtained from (1) and β-mercaptoethanol is probably of this type also.

$$Ar^1NO + \cdot SAr^2 \longrightarrow ArN(O\cdot)-SAr^2 \qquad (9)$$

(iii) *Phenols.*—Several 2,4,6-trialkylphenols are reducing agents active enough to be used technically as inhibitors of autoxidation. As expected available phenols of this type have been found to react with aromatic nitroso-compounds to give aryloxyl radicals [*i.e.* reaction (7), R = ·OAr] which then add to a second molecule of nitroso-compound to give *C*-nitroxides of types (10) or (12) characterized by strong, persistent, and well resolved e.s.r. spectra all having g = 2.006 25 (see Table 3).



(6) R = Bu^t
(7) R = Me
(8) R = OMe

TABLE 3

Splitting constants (mT ±0.01) of nitroxide radicals from 2,4,6-trichloronitrosobenzene and 2,4,6-trisubstituted phenols

			Splitting constants			
2	4	6	a_N	a_{CH_2}	a_{CH}	a_{H_m}
Bu^t	Bu^t	Bu^t	1.285			0.06
Bu^t	MeO	Bu^t	1.29			0.06
Bu^t	Me	Bu^t	1.30	1.00		0.07
Me	Bu^t	Bu^t	1.29	0.87		
Et	Bu^t	Bu^t	1.26		0.49	
Bu^t	Me	Me	1.31	1.00		0.07
Me	Me	Me	1.285	0.92		0.07
Me	Pr	Me	1.30		0.64	
Me	$PhCH_2$	Me	1.30		0.48	

When added in very large excess to (1), 2,4,6-tri-t-butylphenol (6), and 4-methyl- (7) and 4-methoxy-2,6-di-t-butylphenol (8) immediately exhibit the well known[7] e.s.r. spectra of the corresponding aryloxyl radicals (g = 2.0047) with splitting constants in accord with published values. As these spectra slowly decay, those of the nitroxides mentioned above appear (*cf.* Figure 2), increase in intensity during an hour or more, and persist for well over a day. With the other phenols listed in Table 3, which yield aryloxyl radicals having much shorter lifetimes, only the gradual formation and subsequent very slow decay of nitroxide spectra have been noticed. Compound (2) reacts similarly with both (6) and (8) giving rapidly the e.s.r. signals of their aryloxyl radicals which are gradually replaced by wider signals having three groups of lines, that from (6) having a_N 1.26, $a_{H_{o,p}}$ 0.2, a_{H_m} 0.09 mT; g 2.0058, and that from (8) a_N 0.99, a_{H_o} 0.28, a_{H_m} 0.01 mT; g 2.0055. With (7), compound (2) at first gives the e.s.r. spectrum of phenylnitroxide, PhNHO·, which after a day changed to show three overlapping groups of lines having a_N *ca.* 1.1 mT, while 2,4,6-trimethylphenol similarly gives first the phenylnitroxide spectrum and a day later a broad nitroxide spectrum with a_N *ca.* 1.02 mT.

FIGURE 2 E.s.r. spectrum from 2,4,6-trichloronitrosobenzene and 2,4,6-tri-t-butylphenol 45 min after admixture. The asymmetrical centre shows the waning initial signal of the 2,4,6-t-butylphenoxyl radical

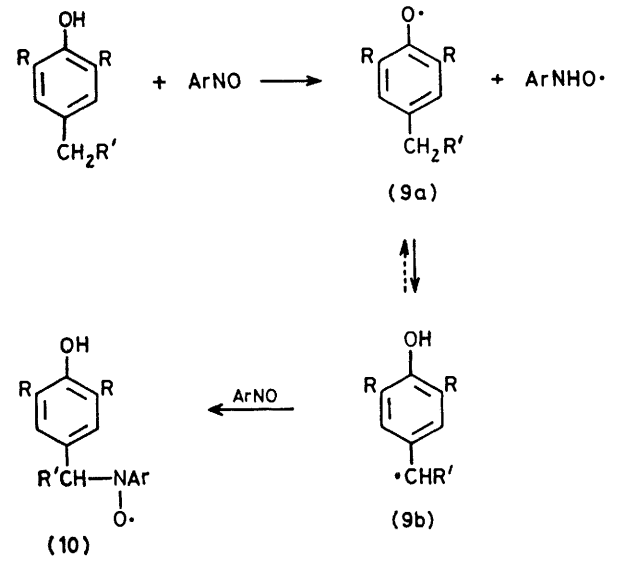
The a_N values (*ca.* 1.3 mT) of the nitroxides listed in Table 3 correspond to those of *C*-nitroxides (*cf.* Table 1) and not to thionitroxides (see above) or oxynitroxides $ArN(O\cdot)OR$,[6,8] both of which have larger a_N splitting values. When the phenol contains a methyl, ethyl, propyl, or benzyl group the eventual nitroxide has evidently been formed by the replacement of an α-hydrogen of the alkyl group to give a radical (9b) of benzylic type (Scheme 2), but with (6) and (8) the nitroxide is evidently (12) formed by nuclear addition as in Scheme 3.

The formation of radicals of both structural types (9b) and (11) by the homolytic oxidation of phenols is well supported by the isolation and structural identification of dimeric and other products from the free radical reactions studied over several years by Waters and his colleagues[9] and by numerous other workers and is now well documented.[10]

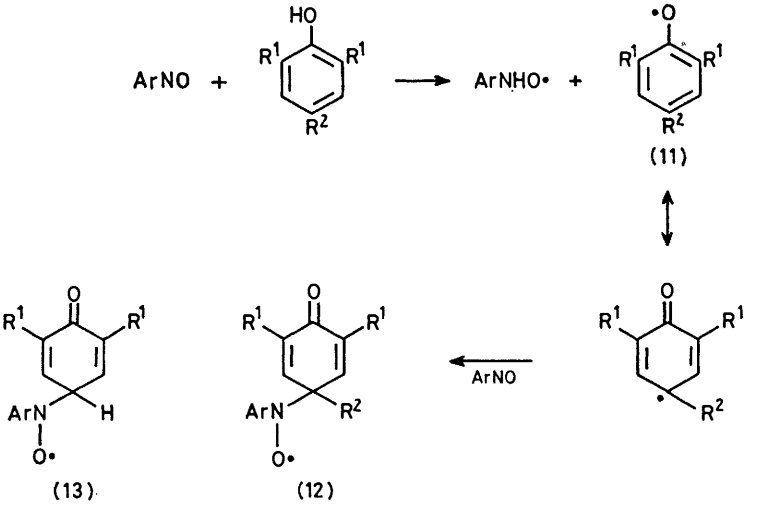
TABLE 4

Splitting constants (mT ±0.02) of nitroxide radicals from 2,4,6-trichloronitrosobenzene and substituted phenols

Substituents and positions				
2	4	6	a_N	a_{CH}
Ph	H	Ph	1.28	0.52
MeO	H	MeO	1.28	0.54
Me	H	Me	1.33	0.62
Bu^t	H	Bu^t	1.30	0.57
Et	H	Et	1.27	0.57
Me	Me	H	1.29	0.53
H	H	Me	*ca.* 1.35	*ca.* 0.6
H	Me	H	1.35	0.62
H	Cl	H	1.32	0.60



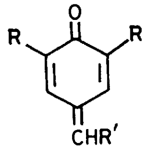
Scheme 2



Scheme 3

Reactions of aryloxyl radicals have been well surveyed by Altwicker.[10] (9a) and (9b) have a common anion and easily disproportionate to the corresponding quinone-methide (14) and the parent phenol. Consequently these quinone-methides might be the true precursors of the nitroxides (10).

Weak nitroxide signals comprised of six broad lines having $g = 2.006\,25$ have also been obtained from (1) and the less substituted phenols listed in Table 4, which are less easily oxidized than those of Table 3 and give aryloxyl radicals detectable only by flow methods.[11] Their splitting constants are in accord with structure (13) which has a $>$CH– group attached to the nitrogen atom. However, other lines appear on storage of the reaction mixtures. This is to be expected since unstable aryloxyl radicals are known to undergo secondary reactions.[10,12] In general the reactivities of (1) and (2) in benzene towards compounds HR are in accord with estimated redox potentials,[13] (1) being the stronger oxidant.



(14)

To summarize the outcome of these exploratory observations which need amplification by both product and kinetic studies, it is evident that though text-books of chemistry stress similarities in behaviour of compounds containing C=O and N=O groups there are important differences between them when both homolytic and heterolytic reactions are considered. Further studies of the reactions of both sections (A) and (B) in a range of solvents are desirable since in polar solvents a transition from homolytic to heterolytic reactivity associated with the nitroso group may well occur for reasons concerned with bond polarity and bond polarizability that have been indicated many years ago.[14]

EXPERIMENTAL

The experimental technique was that of ref. 1, the substrate under investigation always being used in large excess. Liquids were fractionated before use. The substituted phenols were available from previous investigations in this laboratory.

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