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Reactions of Nitrones with Free Radicals. II. Formation of Nitroxides

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Reactions of *N-t*-butylaldonitrones with free radicals gave stable nitroxides, one of which was isolated in pure state. The stability of the nitroxides was explained by the steric effect around the nitrogen and α-carbon atoms. In the reaction of 5,5-dimethyl-Δ^1-pyrroline *N*-oxide with AIBN, nitroxide was detected by ESR technique, and 1,3-adduct and ketonitrone were isolated from the reaction mixture. From the results, it was confirmed that nitroxide is the intermediate of the 1,3-adduct formation and that a radical first adds to the carbon atom and then adds to the oxygen atom of the nitrones.

In the reactions of the aldonitrones with several carbon radicals, we have found new radical 1,3-addition to the carbon and oxygen atoms of the nitrone system.[1] We found that *N-t*-butylaldonitrones and the related compounds reacted with carbon radicals to give extremely stable nitroxides. This paper describes the formation of nitroxides by the addition reactions to the nitrones.[2]

Results and Discussion

Formation of Nitroxides from *N-t*-Butylaldonitrones.

The reaction of α,α′-azobisisobutyronitrile (AIBN) with *N-t*-butyl-α-phenylnitrone (I) in xylene at 110°C gave *N-t*-butyl-*N*-[α-(1-cyano-1-methylethyl)benzyl]nitroxide (III) in a 3.2% yield. Analysis of the ESR spectrum and elemental analysis support the structure (see Table 1 and Experimental). The nitroxide (III) is quite stable to a diffused light, at temperatures below 100°C and also during chromatography on alumina. No change was observed after over one year in air. However, one drop of hydrochloric acid or aqueous sodium hydroxide quenches ESR signals. Addition of one drop of benzyl mercaptan to a benzene solution of III gave almost no change in ESR spectrum, but, when the mixture was warmed for a little while, ESR signals were almost quenched.

The reaction of nitrone I with dimethyl α,α′-

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[1] a) M. Iwamura and N. Inamoto, This Bulletin, **40**, 702 (1967); b) *ibid.*, **43**, 856 (1970).

[2] Preliminary report: M. Iwamura and N. Inamoto, *ibid.*, **40**, 703 (1967).

azobisisobutyrate (MAIB), and the reactions of glyoxal-bis-*N*-*t*-butylnitrone (II) with AIBN or MAIB under similar reaction conditions also gave stable nitroxides (IV—VI), which were detected by ESR spectra but not isolated in pure state. The reaction of nitrone I with tetraphenylsuccinodinitrile at 160°C in *t*-butylbenzene similarly produced the nitroxide VIII. The data are summarized in Table 1.

TABLE 1. ESR SPECTRA OF NITROXIDE RADICALS

Reactant	Nitroxide	a_N*1	a_H*1	Solvent
I+AIBN	III*2	14.6	3.07	THF
I+MAIB	IV	13.4	3.7	Xylene
II+AIBN	V	14.5	0.8	Xylene +o-$Cl_2C_6H_4$
II+MAIB	VI	15.7	*3	Xylene +o-$Cl_2C_6H_4$
I+$PhCHMe_2$ +DTBP	VII	15.1	3.6	$PhCHMe_2$
I+$(Ph_2CCN)_2$	VIII	14.0	8.7	t-C_4H_9Ph

*1 In gauss. *2 g=2.0044.
*3 Not determined because of broadening of signals.

The reaction of nitrone I with di-*t*-butyl peroxide (DTBP) and cumene also gave stable nitroxide (VII) which was detected by means of ESR spectroscopy (Table 1). In the cases of toluene, ethylbenzene and tetralin in the place of cumene, however, ESR spectra showed only triplet, whose splitting constants (a_N) are 14.7, 14.4 and 14.4 gauss, respectively. The structures of the nitroxides remain uncertain. A characteristic common to these cases is that the radicals generated from aralkyl hydrocarbons are $RR'\dot{C}H$; always having at least one α-hydrogen atom. As the nitroxides (IX) are considered to be the intermediate, abstraction of the β-hydrogen atom from the nitroxides (IX) would be easier than that from the starting hydrocarbon $RR'CH_2$, and thus the following reactions would give the nitroxide (X) possessing no α-hydrogen atom.

$$RCH{=}N({\rightarrow}O){-}t\text{-}C_4H_9 + R'\cdot \rightarrow R'RCH{-}N(t\text{-}C_4H_9)O\cdot$$

I: R=Ph
II: R=t-C_4H_9-N(→O)=CH-
III: R=Ph, R′=Me_2CCN
IV: R=Ph, R′=Me_2CCO_2Me
V: R=t-C_4H_9N(→O)=CH-, R′=Me_2CCN
VI: R=t-C_4H_9N(→O)=CH-, R′=Me_2CCO_2Me
VII: R=Ph, R′=$PhCMe_2$
VIII: R=Ph, R′=Ph_2CCN

$$RR'\overset{\beta}{C}H{-}\overset{\alpha}{C}HPh{-}N(t\text{-}C_4H_9){-}O\cdot \xrightarrow{t\text{-}C_4H_9O\cdot}$$
IX

$$RR'\dot{C}{-}CHPh{-}N(t\text{-}C_4H_9){-}O\cdot \xrightarrow{t\text{-}C_4H_9O\cdot}$$
$$RR'C{=}CPh{-}N(t\text{-}C_4H_9){-}O\cdot$$
X

Therefore, it is probable that the detected nitroxides may be the nitroxides X.

Janzen and Blackburn[3] recently reported detection and identification of short-lived free radicals by ESR trapping technique with *N*-*t*-butyl-α-phenylnitrone (I), using our preliminary results.[2] Vincent and Grubbs also reported the formation of the corresponding nitroxide by the reaction of *N*-benzhydryl-α,α-diphenylnitrone with AIBN.[4]

It is known that the reactions of the nitroso compounds with free radicals give trisubstituted hydroxylamines,[5] and that the nitroxides are the intermediate in the above addition reactions.[6]

$$R{-}N{=}O + R'\cdot \rightarrow RR'N{-}O\cdot \xrightarrow{R'\cdot} RR'N{-}OR'$$

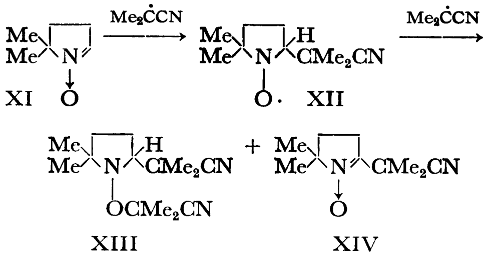
Thus, it is considered that the reactions of the nitrones with free radicals are analogous to those of the nitroso compounds.

After a xylene solution of *N*-benzyl-α-phenylnitrone or glyoxal-bis-*N*-phenylnitrone was heated with AIBN at 130°C for 5 min, ESR spectra were measured immediately, but there was no paramagnetic species, indicating the very short lifetime of the corresponding nitroxides.

Reaction of Δ^1-Pyrroline *N*-Oxides with AIBN. The reaction of 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (XI) with AIBN in xylene at 105—110°C gave a 1,3-adduct (XIII) and a new ketonitrone (XIV). Their yields are listed in Table 2.

TABLE 2. REACTION OF XI WITH AIBN

XI (g)	AIBN (g)	Xylene (m*l*)	Products (%)	
			XIII	XIV
5.65	10	10	47.5	23
2.82	5	10	44.2	6.5



The reactions of 2,4,4-trimethyl- (XV) and 3,3,5,5-tetramethyl-Δ^1-pyrroline *N*-oxides (XVI) with AIBN gave no radical addition product.

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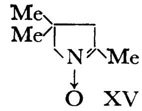
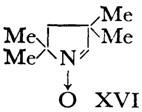
[3] E. G. Janzen and B. J. Blackburn, *J. Amer. Chem. Soc.*, **90**, 5909 (1968).

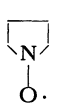
[4] J. S. Vincent and E. J. Grubbs, *ibid.*, **91**, 2022 (1969).

[5] B. A. Gingras and W. A. Waters, *J. Chem. Soc.*, **1954**, 1920.

[6] A. Mackor, Th. A. J. W. Wajer and Th. J. de Boer, *Tetrahedron Lett.*, **1966**, 2115.


XV


XVI


XVII

It was shown by ESR technique that there were two kinds of nitroxides in the reaction mixture of the nitrone (XI) with AIBN. The ESR spectrum of one of the nitroxides showed doublet of triplets ($a_N=14.6$, $a_H=20.4$ gauss), from which the structure was confirmed to be XII by comparison with the hyperfine coupling constants ($a_N=14.9$, $a_H=19.6$ gauss) of pyrrolidine-*N*-oxyl (XVII).[7] Although the nitroxide (XII) was stable at least for two days, it was not isolated by column chromatography on silica gel. The other nitroxide, which is more stable, showed nitrogen splitting constant of 14.6 gauss and no further splitting was observed. The structure remains uncertain.

The results in Table 2 indicate that the radical addition to the nitrone is more favorable than the disproportionation of XII in a lower concentration, and that radical addition is almost independent of concentration. It is plausible that the nitroxide is the intermediate in the radical 1,3-additions and that a radical adds first to the carbon atom of the nitrone group and then to the oxygen atom.

Since ketonitrones did not react with free radicals,[1b] we see that nitrone XV did not give addition product. In the case of nitrone (XVI), it is assumed that the geminal dimethyl groups at the C-3 atom sterically hinder the addition of a radical to the C-2 atom, although the nitroxide derived from XVI would be considered to be very stable if it was once formed.

Stability of Nitroxides. Unhindered aliphatic nitroxides such as dimethylnitroxide[7] or diethylnitroxide[8] are known to decompose through disproportionation. The nitroxides containing aromatic rings such as *N*-*t*-butyl-*N*-phenylnitroxide[9] and diphenylnitroxide[10] decompose to disproportionation products by oxygen-atom transfer.

The stability of bis(trifluoromethyl)nitroxide[11] is attributed to impossibility of disproportionation. The stability of nitroxides such as di-*t*-butylnitroxide[12] and 2,2,5,5-tetramethyl-4-oxopiperidine-*N*-oxyl[13] is attributed to steric effect by bulky groups attached to the nitrogen atom.

It is known that nitroxides having at least one α-hydrogen atom may disproportionate to a nitrone and a hydroxylamine.[7] Recently, it was reported that norpseudopelletierine-*N*-oxyl[14] was stable in spite of the presence of α-hydrogen atom. The reason is attributed to prohibition from the disproportionation by Bredt's rule. Therefore, it is noteworthy that the nitroxides (III—VIII) we obtained are quite stable in spite of the presence of α-hydrogen atom. Thus these nitroxides are a new type of stable nitroxides, and regarded as the first examples of nitroxides prohibited from disproportionation because of a spatial congestion around the α-hydrogen atom.

Although nitroxide XII is similar to the nitroxides (III—VIII) it is less stable. This indicates that the steric effect around the α-carbon atom in XII might be not so large as III—VIII, because the nitroxide group of XII is fixed in the ring.

In conclusion, the aldonitrones react with free radicals to give trisubstituted hydroxylamines as addition product or stable nitroxides, and the difference seems to be explicable in terms of the steric effect around the nitrogen and α-carbon atoms of the nitrone group.

Experimental

Materials. The nitrones were prepared by the methods in literature. *N*-*t*-Butyl-α-phenylnitrone (I),[15] mp 75—76°C; glyoxal-bis-*N*-*t*-butylnitrone,[15] mp 193—194°C; 5,5-dimethyl-Δ^1-pyrroline *N*-oxide,[16] bp 75°C/1.5 mmHg; 2,4,4-trimethyl-Δ^1-pyrroline *N*-oxide,[16] bp 92—95°C/3 mmHg; 3,3,5,5-tetramethyl-Δ^1-pyrroline *N*-oxide,[16] mp 31—32°C. Tetraphenylsuccinodinitrile was prepared by Kharasch's method,[17] mp 217—218°C (dec.).

***N*-*t*-Butyl-*N*-α-(1-cyano-1-methylethyl)benzylnitroxide (III).** Nitrone (I) (4.5 g, 0.025 mol) and AIBN (5 g, 0.03 mol) in xylene (30 m*l*) were heated at 115—120°C until the evolution of nitrogen ceased. Xylene was evaporated *in vacuo* and the reaction mixture was heated at 100—110°C under a pressure of 2 mmHg in order to sublimate most of tetramethylsuccinodinitrile derived from AIBN. The residue was chromatographed on silica gel. Nitroxide (III) was eluted with petroleum ether (bp 30—60°C), and recrystallized from methanol as red needles, mp 121—122°C. λ_{max}^{EtOH}: 437 mμ (ε=22).[*1] Yield 0.2 g (3.2%).

Found: C, 73.25; H, 8.70; N, 11.47%. Calcd for $C_{15}H_{21}N_2O$: C, 73.43; H, 8.63; N, 11.42%.

The analysis of the ESR spectrum in tetrahydrofuran

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[*1] The value reported previously (ε=48)[2] is erroneous.

(THF) is listed in Table 1.

Solutions of Nitroxides. The solutions of nitroxides were prepared by the reaction of *N-t*-butylaldonitrones with an equimolar AIBN or MAIB in a suitable solvent at 110—120°C until the evolution of nitrogen ceased. In the cases of the reactions with DTBP and aralkyl hydrocarbons, the solutions of nitroxides were prepared by the reaction of nitrone I (*ca.* 0.2 g) with an aralkyl hydrocarbon (5 m*l*) and DTBP (1 m*l*) at 130—140°C for 1.5 hr. In the reaction of nitrone (I) with tetraphenylsuccinodinitrile, the equimolar mixture was heated in *t*-butylbenzene at 160°C for 2 hr. After the reaction had completed, the reaction mixture was transferred to an ESR sampling tube and then ESR spectra were taken after evacuation. To avoid any broadening due to dipole-dipole interaction, the reaction mixture was sometimes diluted with the dry solvent.

ESR Measurement. ESR spectra were taken on an X-band TES-3B spectrometer. Calibration was carried out with the NMR signal of water.

Reaction of 5,5-Dimethyl-Δ^1-pyrroline *N*-Oxide (XI) with AIBN. A typical procedure is as follows. *N*-Oxide (5.65 g, 0.05 mol) and AIBN (10 g, 0.06 mol) were dissolved in 10 m*l* of xylene and the solution was heated at 105—110°C with stirring until the evolution of nitrogen ceased. Xylene was evaporated *in vacuo* and the reaction mixture was chromatographed on silica gel. With petroleum ether, 7 g of the 1,3-adduct (XIII) (47.5%) was eluted. Tetramethylsuccinodinitrile (3.8 g) was eluted with benzene. A small amount of the starting *N*-oxide was eluted with ether, and the nitrone (XIV) (2.7 g, 23%) was eluted with acetone. The crude 1,3-adduct (XIII) was recrystallized from benzene, mp 88—88.5°C. NMR (in CCl_4): δ 1.23 (3H), 1.32 (3H), 1.35 (3H), 1.45 (3H), 1.69 (3H), 1.74 (3H), 1.2—1.8 (4H, broad), and 3.34 (1H, multiplet).

Found: C, 67.45; H, 9.33; N, 16.92%. Calcd for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85%.

The crude nitrone (XIV) was recrystallized from benzene and methanol, mp 93.5—94.5°C. NMR (in CCl_4): δ 1.35 (6H), 1.70 (6H), 2.02 (2H, triplet, J=7.5 Hz), and 2.78 (2H, triplet, J=7.5 Hz).

Found: C, 66.83; H, 8.95; N, 15.43%. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55%.