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Reactions of Nitrones with Free Radicals. I. Radical 1,3-Addition to Nitrones

Michiko IWAMURA and Naoki INAMOTO

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo

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Reactions of the aldonitrones with α,α′-azobisisobutyronitrile or dimethyl α,α′-azobisisobutyrate gave trisubstituted hydroxylamines as addition products, whose structures were determined to be radical 1,3-addition products to the nitrones. Reactions of *N*-benzyl-α-phenylnitrone with di-*t*-butyl peroxide and aralkyl hydrocarbons possessing at least one α-hydrogen atom gave similar 1,3-adducts and substituted *N*-benzylaldonitrones. Reaction of α,*N*-diphenylnitrone with phenylazotriphenylmethane gave similarly α,α,*N*-triphenylnitrone. Mechanisms for the formation of these products were discussed.

Inamoto and Simamura found that the reaction of α,α′-azobisisobutyronitrile (AIBN) with nitrobenzene at 100°C gave *N*,*O*-bis(1-cyano-1-methylethyl)phenylhydroxylamine, acetone and hydrogen cyanide in 3% yields.[1,2] In the reaction of AIBN with azoxybenzene or *N*,*N*-dimethylaniline *N*-oxide at 100°C, azobenzene or *N*,*N*-dimethylaniline was isolated in 1—1.5% yield, together with acetone (1—1.5%) and hydrogen cyanide.[3] From the results it was considered that the free radicals generated from AIBN are able to abstract the oxygen atom from some N→O bonds by addition-elimination mechanism.

In connection with the results, the reactions of AIBN or related compounds with aldonitrones were attempted. It was found that two 1-substituted 1-methylethyl radicals add to the nitrones in good yields.[4] This paper describes the addition reactions of free radicals to nitrones in detail.

Results and Discussion

Addition of Free Radicals Generated from Aliphatic Azo Compounds. When AIBN was decomposed in xylene containing an equimolar amount of α,*N*-diphenylnitrone (I) at 90—110°C, an addition product (IV) was obtained in 63% yield. Similar addition products were obtained in the reactions of *N*-benzyl-α-phenylnitrone (II) and glyoxal-bis-*N*-phenylnitrone (III). In the case of the dinitrone (III), an addition product to only one nitrone group was produced even with an excess of AIBN. Dimethyl α,α′-azobisisobutyrate (MAIB) behaved similarly as a radical source under similar conditions. The results are summarized in Table 1.

Table 1. Addition products of 1-substituted 1-methylethyl radicals to nitrones

	Addition product		Elemental analysis (%)			
	%	Mp (°C)		C	H	N
IV	63	142.5—143.5	Found	75.52	6.86	12.65
			Calcd	75.64	6.95	12.65
V	46	114—115	Found	75.94	7.54	12.09
			Calcd	76.05	7.25	12.10
VI	50	55—56	Found	69.47	7.56	3.69
			Calcd	69.15	7.32	3.51
VII	40	51—52	Found	69.56	7.53	3.40
			Calcd	69.71	7.56	3.39
VIII	15	134—134.5	Found	70.24	6.55	15.17
			Calcd	70.18	6.43	14.88

In these reactions, it is required that the nitrones are stable under the reaction conditions. However, most of the nitrones are susceptible to heat and

$$RCH{=}N(\rightarrow O)R' + 2Me_2\dot{C}X \rightarrow RCH(CMe_2X)\text{–}NR'\text{–}OCMe_2X$$

I: R=R′=Ph
II: R=Ph, R′=$PhCH_2$
III: R=PhN(→O)=CH–, R′=Ph

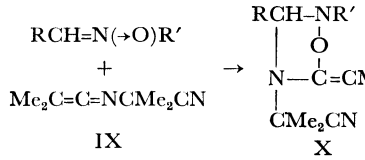
IV: R=R′=Ph, X=CN
V: R=Ph, R′=$PhCH_2$, X=CN
VI: R=R′=Ph, X=CO_2Me
VII: R=Ph, R′=$PhCH_2$, X=CO_2Me
VIII: R=PhN(→O)=CH–, R′=Ph, X=CN

1) N. Inamoto and O. Simamura, *J. Org. Chem.*, **23**, 408 (1958).
2) N. Inamoto, *Yuki Gosei Kagaku Kyokai Shi*, **16**, 420 (1958).
3) N. Inamoto, *ibid.*, **17**, 170 (1959).
4) Preliminary report: M. Iwamura and N. Inamoto, This Bulletin, **40**, 702 (1967).

undergo isomerization to amides or decomposition.[5] Therefore, the aliphatic aldonitrones were not used.

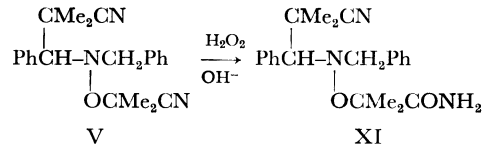
Structure of Addition Products. Elemental analyses (see Table 1), NMR and IR spectra of the addition products (IV—VIII) support the proposed structures, trisubstituted hydroxylamines. For example, the NMR spectrum of IV in deuteriochloroform showed signals at δ 1.14 (3H), 1.35 (3H), 1.75 (3H), 1.95 (3H), 3.50 (1H, broad), 6.88, 7.05, 7.08 (5H in total), and 7.19 (5H), and the IR spectrum in KBr disk showed absorption peaks at 2220 (CN), 1592, 1277, 1220, 1198, 1160, 1083, 1030, 1015, 970, 950, 925, 915, 902, 890, 764, 740, 713, and 700 cm^{-1} (phenyl and trisubstituted hydroxylamine[6]).

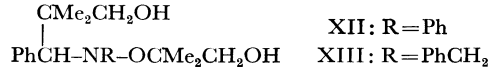
However, some uncertainty remains in the cases of IV, V and VIII for the following reason. It is known that the decomposition of AIBN gives the keteneimine (IX) as an intermediate.[7,8] The nitrones are well known as 1,3-dipolar substrates.[9] If the nitrones react with IX by 1,3-dipolar cycloaddition, it would be expected to yield a five-membered ring compound such as X, which has the same molecular formula as the radical addition product.



Distinction between the two or more structures was difficult from only the spectral data. Thus dimethyl-*N*-(1-cyano-1-methylethyl)keteneimine (IX) was allowed to react with the nitrone (II) at room temperature for two days. However, only the same compound as the radical addition product (V) was obtained from the reaction mixture, and it was impossible to determine the structure by this method.

The addition product (IV) gave hydrogen cyanide and acetone by heating with hydrochloric acid in ethanol. This fact indicates that one 1-cyano-1-methylethyl group was attached to the oxygen or nitrogen atom. Treatment of the compound (V) with an alkaline hydrogen peroxide gave a nitrile-amide (XI), which was inert to an alkaline hydrogen peroxide even under more vigorous conditions. If the structure (V) is correct, the structure of the nitrile-amide is assumed to be XI, because the 1-cyano-1-methylethyl group bonded to the oxygen atom seems to be sterically more favorable for hydrolysis. These facts support the structures, IV and V, rather than the structure X. However, several attempts to correlate the cyano compound (IV or V) to the methoxycarbonyl compound (VI or VII) were unsuccessful.

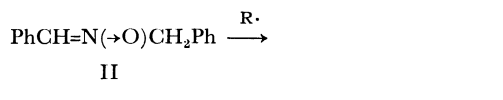




Compound (VI) was reduced with lithium aluminum hydride to a diol (XII). The same treatment of compound (VII) was assumed to afford diol (XIII), but pure substance was not obtained.

1-Methoxycarbonyl-1-methylethyl radicals generated from MAIB can not give a keteneimine type of intermediate. Similar addition products were also obtained by the reactions of MAIB with nitrones. As an example, the NMR spectrum of VI in carbon tetrachloride exhibited signals at δ 0.85 (3H), 1.24 (3H), 1.42 (3H), 1.52 (3H), 2.99 (3H), 3.75 (3H), 4.55 (1H, broad), 6.97 (5H), and 7.10 (5H). Therefore, it is reasonable that the addition products (IV—VIII) are trisubstituted hydroxylamines produced by the 1,3-addition of two radicals to the carbon and oxygen atoms in the nitrone system.

Addition of Other Carbon Radicals. The reaction of *N*-benzyl-α-phenylnitrone (II) with di-*t*-butyl peroxide (DTBP) in *t*-butylbenzene at 135°C for 12 hr gave only the decomposition products and no starting nitrone was recovered. In the aralkyl hydrocarbons possessing at least one α-hydrogen, however, reaction products with radicals were isolated. In these cases, nitrone II was mainly used, because it is considerably stable during heating for a long time. Toluene, ethylbenzene, isopropylbenzene, tetralin and diphenylmethane were used as aralkyl hydrocarbons. These facts show that the nitrones have an ability as a radical scavenger.



XIVa: R=$PhCH_2$ XVa: R=$PhCH_2$
XIVb: R=PhCHMe XVb: R=PhCHMe
XIVc: R=$PhCMe_2$
XIVd: R=$C_{10}H_{11}$ XVd: R=$C_{10}H_{11}$
($C_{10}H_{11}$: α-tetralyl) XVe: R=Ph_2CH

As the reaction products, an addition product (XIV) and a new aldonitrone (XV) were isolated from the reaction mixture in the cases of most

5) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).
6) B. A. Gingras and W. A. Waters, *J. Chem. Soc.*, **1954**, 1920.
7) M. Talât-Erben and S. Bywater, *J. Amer. Chem. Soc.*, **77**, 3710, 3712 (1955).
8) G. S. Hammond, C. S. Wu, D. O. Trapp, J. Warkentin and R. T. Keys, *ibid.*, **82**, 5394 (1960).
9) R. Huisgen, *Angew. Chem.*, **75**, 604, 741 (1963).

aralkyl hydrocarbons described above. However, the new aldonitrone was not isolated in the case of isopropylbenzene, and the addition product derived from diphenylmethane was not detected. The results and elemental analyses of XIV and XV are summarized in Tables 2 and 3.

Table 2. Reaction products of aralkyl radicals to nitrone (II) at 135°C

Radical	Reaction condition*	Addition product (XIV) Yield (%)	Addition product (XIV) Mp (°C)	Nitrone (XV) Yield (%)	Nitrone (XV) Mp (°C)
$PhCH_2\cdot$	a)**	2.6	79—86.5	6.2	152.5—153.5
PhCHMe·	a)	29	oil	17	181—184
	b)	60		5	
$PhCMe_2\cdot$	a)	35	oil	—	
	b)	47		—	
	a)	59	oil	15	148.5—150
	b)	79		8	
$Ph_2CH\cdot$	b)	—		trace	187—189

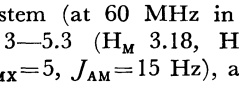
* a) II (0.01 mol), DTBP (0.03 mol), and RH (25 ml)
b) II (0.01 mol), DTBP (0.02 mol), and RH (0.2 mol)
** At the refluxing temperature

Table 3. Elemental analyses of XIV and XV

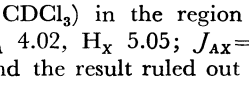
		Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
Addition product (XIV)							
XIVa	$C_{28}H_{27}NO$	85.46	6.92	3.56	85.53	7.00	3.53
XIVb	$C_{30}H_{31}NO$	85.47	7.41	3.80	85.43	7.12	3.53
XIVc	$C_{32}H_{35}NO$	85.48	7.85	3.12	85.42	7.98	2.97
XIVd	$C_{34}H_{35}NO$	86.21	7.45	2.96	86.24	7.63	3.02
Nitrone (XV)							
XVa	$C_{21}H_{19}NO$	83.69	6.35	4.65	83.48	6.28	4.63
XVb	$C_{22}H_{21}NO$	83.77	6.71	4.44	83.90	6.54	4.18
XVd	$C_{24}H_{23}NO$	84.42	6.79	4.10	84.45	6.69	3.89
XVe	$C_{27}H_{23}NO$	85.91	6.14	3.71	85.76	5.99	3.60

The addition products (XIV) are determined to be 1,3-radical addition products, trisubstituted hydroxylamines, from the spectral data. All the 1,3-adducts except for that derived from toluene are colorless oils.

The structures of the new aldonitrones (XV) were confirmed by NMR spectra. For instance, the NMR spectrum of XVa shows an AMX spin system (at 60 MHz in $CDCl_3$) in the region of δ 3—5.3 (H_M 3.18, H_A 4.02, H_X 5.05; $J_{AX}=9$, $J_{MX}=5$, $J_{AM}=15$ Hz), and the result ruled out an isomeric structure (XVI).



XVI



XVa

The nitrones (XVa, XVb, and XVd) have the coupling constant J_{AX} of about 10 Hz, indicating that H_A and H_X are located in a *trans* position to each other.

A similar reaction was attempted with α,N-diphenylnitrone (I), using isopropylbenzene or tetralin as an aralkyl hydrocarbon. In both cases, crude 1,3-adducts were obtained as viscous oil by means of column chromatography, but attempts to isolate pure adducts were unsuccessful.

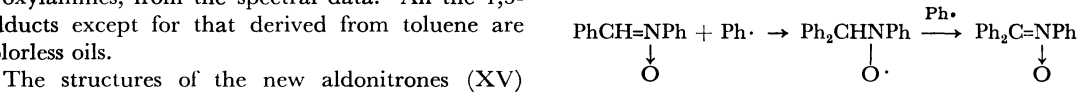
As seen from Table 2, the yields of the 1,3-adduct are affected by the amount of DTBP; that is, the yields are better in condition b), where a smaller amount of DTBP was used, than in condition a). The results indicate that the addition reaction to the nitrone competes with decomposition of the nitrones by DTBP.

Reaction of α,N-diphenylnitrone (I) with phenylazotriphenylmethane in refluxing benzene gave α,α,N-triphenylnitrone.

Formation Mechanism. It was confirmed that the rate of evolution of nitrogen gas from AIBN was almost the same either in the presence or in the absence of the nitrones. This finding shows that the nitrones react with free radicals generated from AIBN.

As the addition products are trisubstituted hydroxylamines, it is reasonable to consider that two radicals could add to the nitrones in a 1,3-fashion. It has been found that nitroxides were formed instead of expected trisubstituted hydroxylamines in the cases of the *N-t*-butylnitrones.[10] In the reaction of a cyclic nitrone, 5,5-dimethyl-Δ^1-pyrroline *N*-oxide, with AIBN, it was confirmed by ESR technique that nitroxide was the intermediate of the 1,3-adduct.[10] These facts indicate that, in the reaction of the nitrones with free radicals, radicals first add to the carbon atom and then to the oxygen atom of the nitrone system.

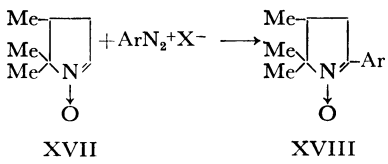
The fact that the reaction of α,N-diphenylnitrone (I) with phenyl radical generated from phenylazotriphenylmethane gave α,α,N-triphenylnitrone supports that a radical first adds to the carbon atom to produce nitroxide radical, from which reactive phenyl radical abstracts a hydrogen atom to afford a new ketonitrone, as shown below.



It was recently reported that the reaction of 4,5,5-trimethyl-Δ^1-pyrroline *N*-oxide (XVII) with substituted benzenediazonium salts gave the 2-aryl derivatives (XVIII) in the presence of sodium acetate, sodium sulfite and cupric sulfate.[11]

10) Preliminary report: M. Iwamura and N. Inamoto, This Bulletin, **40**, 703 (1967); *ibid.*, **43**, 860 (1970). (Part II).

11) R. F. C. Brown, L. Subrahmanyan, and C. P. Whittle, *Aust. J. Chem.*, **20**, 339 (1967).



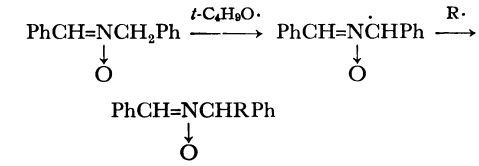
XVII XVIII

This result also supports the mechanism mentioned above.

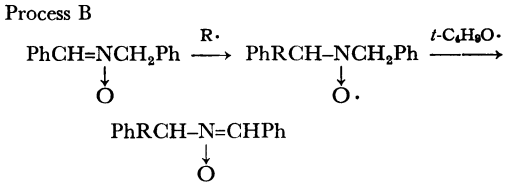
The ketonitrone such as α,*N*-dimethyl-α-phenylnitrone, did not afford a 1,3-adduct with AIBN. This result is analogous to the fact that Grignard reagents add to the aldonitrones in a 1,3-fashion but the reactions with ketonitrones produce Schiff bases.[5]

As for the mechanism of the formation of the new aldonitrones in the reactions of nitrone II with DTBP and aralkyl hydrocarbons, the following two processes might be conceivable.

Process A



Process B



If the nitroxide was assumed to be a common intermediate in formation of both nitrone and 1,3-adduct as shown in Process B, the nitroxide might afford an isomeric ketonitrone instead of the isolated aldonitrone, because abstraction of a tertiary hydrogen atom is usually easier than that of a secondary one. Therefore, it is considered that Process A might be more reasonable than Process B.

Experimental

Materials. Commercial α,α′-azobisisobutyronitrile (AIBN) was recrystallized from ethanol, mp 103—105°C. Dimethyl α,α′-azobisisobutyrate (MAIB) was prepared from AIBN,[12] mp 29—31°C. Commercial di-*t*-butyl peroxide (DTBP) was dried over anhydrous calcium chloride and distilled at 21—22°C/17 mmHg. Benzene, toluene, xylene, ethylbenzene, cumene, tetralin, and diphenylmethane were used after usual purification. Phenylazotriphenylmethane was prepared by Gomberg's method,[13] mp 111—112°C (dec). Nitrones were prepared by the methods described in literature: α,*N*-diphenylnitrone (I),[14] mp 112—114°C; *N*-benzyl-α-phenylnitrone (II),[15] mp 81—83°C; glyoxal-bis-*N*-phenylnitrone (III),[16] mp 181—182°C; α,*N*-dimethyl-α-phenylnitrone,[17] mp 113—114°C.

Addition Reactions of Nitrones with AIBN. A typical procedure is described for α,*N*-diphenylnitrone (I). Nitrone I (18.7 g, 0.1 mol) in 80 m*l* of xylene was heated on a steam bath and AIBN (15.6 g, 0.1 mol) was added little by little to the solution. The mixture was heated for 7 hr, and distilled with steam. Acetone was isolated as its 2,4-dinitrophenylhydrazone (0.22 g, 0.924 mmol, 0.46%) from the distillate. From the residue, a crude addition product (IV), which was recrystallized from methanol, was obtained in a 63% yield (19.8 g). The same product (IV) could be isolated by the following procedure. From the reaction mixture, xylene and other volatile compounds were distilled off under reduced pressure, and then petroleum ether was added to the residue. The precipitate thus obtained was recrystallized from methanol. The results are summarized in Table 1.

Addition Reactions of Nitrones with MAIB. A typical procedure is described for the reaction of *N*-benzyl-α-phenylnitrone (II). Nitrone (II) (7.0 g, 0.033 mol) and MAIB (7.0 g, 0.030 mol) in 35 m*l* of xylene were heated at 120—125°C with stirring. After the evolution of nitrogen gas had ceased, xylene and other volatile components were distilled off *in vacuo*. The residual oil was chromatographed on silica gel with petroleum ether (60—80°C). From the fractions eluted with petroleum ether, 8 g of colorless oil was obtained. The IR spectrum of this oil was different from that of the dimethyl tetramethylsuccinate derived from MAIB. After standing for ten days, it solidified, and then was recrystallized from petroleum ether. The results are summarized in Table 1.

Decomposition of Adduct (IV) with Hydrochloric Acid. IV (1.2 g) dissolved in 30 m*l* of 10% aqueous hydrochloric acid by adding ethanol was refluxed for 10 hr, during which hydrogen cyanide was detected. From the ethanol distilled from the reaction mixture, acetone was detected as its 2,4-dinitrophenylhydrazone (70 mg).

Formation of Nitrile-amide (XI) from Adduct V. V (7.0 g, 0.021 mol) was dissolved in 48 m*l* of 10% hydrogen peroxide containing 2 m*l* of 6N sodium hydroxide by adding 200 m*l* of ethanol. The solution was heated at 50°C for 2 days, and then poured into 500 m*l* of water. Crude nitrile-amide (6.5 g, 89%) was collected by filtration and recrystallized from 95% ethanol, mp 182.5—183°C. IR (in Nujol): 3500(NH), 3180(NH), 2230(C≡N), and 1690 cm^{-1} (C=O).

Found: C, 72.56; H, 7.47; N, 11.62%. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50%.

Formation of Diol (XII) from Adduct VI. An anhydrous ether solution of VI (2 g, 0.005 mol) and lithium aluminum hydride (0.4 g, 0.01 mol) was refluxed for 4 hr. The excess lithium aluminum hydride was decomposed by ethyl acetate and the solution was poured into alkaline water. The solution was extracted

12) J. Thiele and K. Hauser, *Ann. Chem.*, **290**, 1 (1896).
13) M. Gomberg, *Ber.*, **30**, 2043 (1897).
14) G. E. Utzinger, *Ann. Chem.*, **556**, 50 (1944).
15) H. E. De La Mare and G. M. Coppinger, *J. Org. Chem.*, **28**, 1068 (1963).
16) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1892 (1954).
17) O. Exner, *Collect. Czech. Chem. Commun.*, **16**, 258 (1951); *Chem. Abstr.*, **47**, 5884 (1953).

with ether and dried over anhydrous magnesium sulfate. By chromatography on silica gel and then recrystallization from benzene and petroleum ether, 1 g of diol (XII) was obtained, mp 89—90°C. NMR (in $CDCl_3$): δ 0.84 (3H), 1.10 (3H), 1.15 (3H), 1.20 (3H), 2.98, 3.23, 3.42, 3.70, 3.88 ($2CH_2+2OH$, 6H in total), 4.08 (1H), 7.00 (5H), and 7.12 (5H).

Found: C, 73.14; H, 8.58; N, 4.07%. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08%.

Reaction of Nitrone II with Aralkyl Hydrocarbons and DTBP. A typical procedure is described for the reaction of II with ethylbenzene and DTBP. A mixture of II (32.11 g, 0.01 mol), ethylbenzene (21.2 g, 0.2 mol) and DTBP (2.90 g, 0.02 mol) was heated at 135°C for 12 hr under nitrogen with frequent shaking. Ethylbenzene and other volatile products were then distilled off under reduced pressure. The residue was chromatographed on silica gel. With petroleum ether-benzene, 2,3-diphenylbutane was eluted and then 2.56 g of addition product (XIVb) was eluted. With benzene-ethyl ether, nitrone (XVb) (0.18 g) was eluted. After XVb had been eluted, a small amount of II was eluted. The crude addition product (XIVb) was diluted with ethyl ether dried over anhydrous sodium sulfate. Ether was then evaporated and XIVb was dried *in vacuo* under nitrogen. The crude nitrone (XVb) was recrystallized from benzene and petroleum ether. The results are summarized in Tables 2 and 3.

Reaction of Nitrone I with Phenylazotriphenylmethane. Phenylazotriphenylmethane (7.4 g, 0.021 mol) was allowed to react with a solution of the nitrone I (4.2 g, 0.021 mol) in 80 m*l* of benzene for 2 hr at 70—80°C with stirring under argon atmosphere. After addition of petroleum ether, precipitates thus obtained (mainly α,α,N-triphenylnitrone) were recrystallized from benzene as white needles, mp 216—219°C (dec.) (lit, 216—217°C (dec.)[18] or 220°C[19]). Yield 2.2 g (38%) (Found: C, 83.64; H, 5.72; N, 5.09%). This reaction was carried out qualitatively, and no further treatment was done.

18) H. Staudinger and K. Miescher, *Helv. Chim. Acta*, **2**, 568 (1919).

19) A. Dornow, H. Gehrt and F. Ische, *Ann. Chem.*, **585**, 226 (1954).