Oxidation of N,N-Dialkyl Hydroxylamines with *t*-Butyl Hydroperoxide. A New Synthesis for Nitrones

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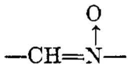
N,N-Dibenzylhydroxylamine has been oxidized by *t*-butyl hydroperoxide to the corresponding nitrone in excellent yield. The oxidation of an aliphatic hydroxylamine, N,N-diethylhydroxylamine, has also been carried out. However, in the latter case the nitrone was not isolated as such but trapped *in situ* to give the isoxazolidine. Chemical evidence and electron magnetic resonance measurements suggest a unique free radical mechanism.

In the course of mechanistic investigations of amine-hydroperoxide interaction, specifically those of dialkylamines, a hydroxylamine intermediate has been considered.[1] The fate of such an intermediate has been previously obscured because of the large excess of amine present in such reactions. To settle this question, the oxidations of an N,N-diaralkyl and an N,N-dialkylhydroxylamine have now been examined in an inert solvent.

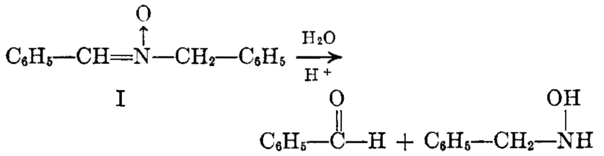
Results

N,N-Dibenzylhydroxylamine.—The reaction of N,N-dibenzylhydroxylamine and *t*-butyl hydroperoxide was carried out in benzene solution (55°). The crystalline product displayed absorption bands in the infrared which have been assigned to the nitrone group, 6.29 μ, 6.35 μ[2]; the ultraviolet spectrum also showed a characteristic band at 300 mμ.[3]



$$-\mathrm{CH}{=}\overset{\overset{\mathrm{O}}{\uparrow}}{\mathrm{N}}-$$

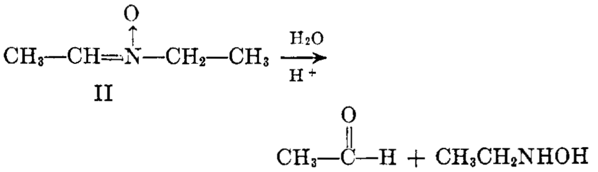
The nitrone was hydrolyzed in acid media to yield benzaldehyde which was identified as the 2,4-dinitrophenylhydrazone.



$$\underset{\mathrm{I}}{C_6H_5-CH{=}\overset{\overset{O}{\uparrow}}{N}-CH_2-C_6H_5} \xrightarrow[H^+]{H_2O} C_6H_5-\overset{\overset{O}{\|}}{C}-H + C_6H_5-CH_2-\overset{\overset{OH}{|}}{N}H \quad (1)$$

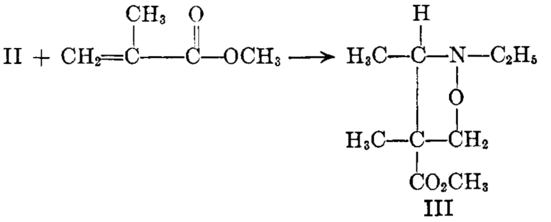
Further confirmation of structure I was effected by reduction of the product to dibenzylhydroxylamine with lithium aluminum hydride. Finally the combustion analysis was consistent with the assignment of a nitrone structure (I) to this product.

N,N-Diethylhydroxylamine.—N,N-Diethylhydroxylamine reacted rapidly with *t*-butyl hydroperoxide in benzene (25°). It was not possible to isolate the nitrone by distillation. However, it was possible to demonstrate that a nitrone was formed by treating the crude benzene reaction mixture with 2,4-dinitrophenylhydrazine in acid media to confirm that hydrolysis of the reaction product produced acetaldehyde.



$$\underset{\mathrm{II}}{CH_3-CH{=}\overset{\overset{O}{\uparrow}}{N}-CH_2-CH_3} \xrightarrow[H^+]{H_2O} CH_3-\overset{\overset{O}{\|}}{C}-H + CH_3CH_2NHOH \quad (2)$$

Recent work[4] on the addition of nitrones to olefins suggested the possibility of trapping the nitrone II by reaction with methyl methacrylate to give the isoxazolidine, III.

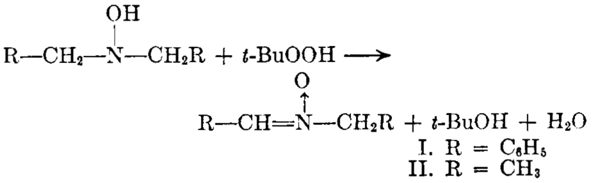


(3)

Such a trapping technique permitted the isolation of III (mixture of two isomers) in 75% yield. The isolation of III confirms the structure of the intermediate nitrone as II.

Discussion

The stoichiometry of the dialkylhydroxylamine oxidation in inert solvent is closely approximated by equation 4, the crude nitrone being isolated in ~90% yield in the case of the more easily isolable crystalline nitrone, I. Electron magnetic resonance measurements on the reaction indicate that there is an intermediate free radical. The structure of the free radical has been determined to be as follows.



$$R-CH_2-\overset{\overset{OH}{|}}{N}-CH_2R + t\text{-BuOOH} \longrightarrow R-CH{=}\overset{\overset{O}{\uparrow}}{N}-CH_2R + t\text{-BuOH} + H_2O \quad (4)$$

$$\text{I. } R = C_6H_5 \qquad \text{II. } R = CH_3$$

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[1] (a) G. M. Coppinger and J. D. Swalen, *J. Am. Chem. Soc.*, **83**, 4900 (1961); (b) H. E. De La Mare, *J. Org. Chem.*, **25**, 2114 (1960).

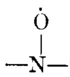
[2] L. G. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 115, 305.

[3] M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 566 (1957). Kamlet and Kaplan report disappearance of the "K band" (314 to 352 mμ) as a result of a photochemical destruction of the nitrone group. We have observed a similar photochemical destruction of I in this current work. A dilute solution of I in benzene showed the following rate of disappearance in ordinary light at room temperature:

Time, hr.	A_{300} mμ
0	0.71
24	.55
96	.19

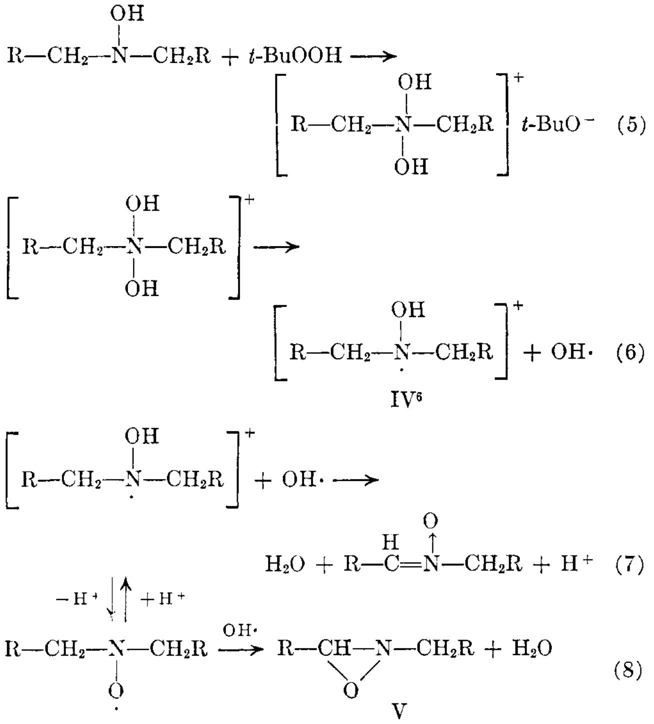
Similar behavior was also noted in dilute isoöctane solutions.

[4] (a) R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters*, No. **12**, 9 (1960); (b) N. A. Le Bel, J. J. Whang, *J. Am. Chem. Soc.*, **81**, 6334 (1959); (c) C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Taylor, and R. Wright, *Proc. Chem. Soc.*, 254 (1960).



$$\overset{\dot{O}}{\overset{|}{—N—}}$$[5]

We suggest that the following mechanism is consistent with these observations.



$$R—CH_2—\overset{OH}{\overset{|}{N}}—CH_2R + t\text{-BuOOH} \longrightarrow \left[R—CH_2—\underset{OH}{\underset{|}{\overset{OH}{\overset{|}{N}}}}—CH_2R\right]^+ t\text{-BuO}^- \quad (5)$$

$$\left[R—CH_2—\underset{OH}{\underset{|}{\overset{OH}{\overset{|}{N}}}}—CH_2R\right]^+ \longrightarrow \underset{IV^6}{\left[R—CH_2—\underset{\cdot}{\overset{OH}{\overset{|}{N}}}—CH_2R\right]^+} + OH\cdot \quad (6)$$

$$\left[R—CH_2—\underset{\cdot}{\overset{OH}{\overset{|}{N}}}—CH_2R\right]^+ + OH\cdot \longrightarrow H_2O + R—\overset{H}{C}=\overset{O}{\overset{\uparrow}{N}}—CH_2R + H^+ \quad (7)$$

$$-H^+ \downarrow\uparrow +H^+$$

$$R—CH_2—\underset{\underset{\cdot}{O}}{\underset{|}{N}}—CH_2R \xrightarrow{OH\cdot} \underset{V}{R—CH—N—CH_2R} + H_2O \quad (8)$$

One might expect the oxazirane (V) as a primary product along with the nitrone, but the best preliminary evidence is that it is not formed.[7]

An interesting corollary of our studies of amine–hydroperoxide reactions is the observation that N,N-dialkyl hydroxylamines react much more rapidly with *t*-butyl hydroperoxide than the analogous dialkylamines.[1b] If one assumes that the first step in both reactions is a nucleophilic displacement (equation 5) by amino nitrogen on the O—O bond, then this is a clear demonstration of the Pearson–Edwards[8] "alpha" effect. At equal molarities (0.6 *M*) the reaction of N,N-diethylhydroxylamine and *t*-butyl hydroperoxide is roughly 35% complete in one hour at 25°. In contrast, our measurements indicate that the reaction between diethylamine and *t*-butyl hydroperoxide is exceedingly slow at 25°; in fact, no detectable reaction was observed in 120 hours. That hydroxylamines are not important products in oxidations conducted in excess *N*,*N*-dialkylamines[1] is consistent with the highly nucleophilic character of the former as opposed to the amine.

Experimental

Materials. N,N-Dibenzylhydroxylamine.—Dibenzylhydroxylamine was prepared[9] by heating together 1 mole of benzylchloride, 0.5 mole of hydroxylamine hydrochloride, and 1.5 moles of sodium carbonate in 2 l. of methanol–water (75–25) for a period of 4 hr. The reaction mixture was extracted with ether. The product was recovered from the ether solution and recrystallized from isoöctane; yield ~50% (m.p. 123–124°).

N,N-Diethylhydroxylamine.—Diethylhydroxylamine was purchased from the Aldrich Chemical Co. The crude material was employed in preliminary studies; however, carefully fractionated material[10] [b.p. 82–83° (108 mm.), $n^{25}D$ 1.4176] was employed for the isoxazolidine preparation.

***t*-Butyl Hydroperoxide.**—*t*-Butyl hydroperoxide of high purity was prepared by careful vacuum fractionation of commercial stock (Lucidol). All other chemicals were of reagent grade quality.

N,N-Diethylamine.—Diethylamine (Matheson, Coleman & Bell) was distilled from calcium hydride just prior to use.

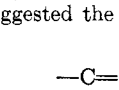
Analyses.—Spectral analyses were made on the Perkin-Elmer 21 and the Cary Model 14 spectrophotometers. The Hy-Fi (Wilkens Instrument) flame ionization instrument was used for gas–liquid chromatographic (g.l.c.) analyses.

Reaction of N,N-Dibenzylhydroxylamine and *t*-Butyl Hydroperoxide.—N,N-Dibenzylhydroxylamine (7.65 g., 0.037 mole) reacted with *t*-butyl hydroperoxide (3.52 g., 99 wt. %; 0.039 mole) in 60 ml. of benzene. After approximately 3 hr. at 55° and 5.5 hr. at gentle reflux, the reaction mixture (benzene phase)[11] contained no peroxide as evidenced by the disappearance of the peroxide band at 11.85 μ in the infrared.[2] New bands appeared at 6.30, 6.38, and ~11 μ. The 11-μ band arises from the presence of *t*-butyl alcohol as a reaction product.

Distillation and g.l.c. analysis of the volatile products showed only benzene and *t*-butyl alcohol (0.033 mole by lithium aluminum hydride analysis) to be present. A white solid residue remained after distillation (weight of crude 7.25 g.; m.p. 73–76°). Recrystallization of the crude solid from benzene–petroleum ether gave 6.1 g. of product, m.p. 82–83°.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.6; H, 6.20; N, 6.63. Found: C, 79.0; H, 6.1; N, 6.6.

Infrared spectral analysis of a recrystallized sample showed a strong band at 6.29 μ with a shoulder at 6.35 μ. The strong absorption at 6.29 suggested the presence of the nitrone group,



$$—C=\overset{O}{\overset{\uparrow}{N}}—$$

The ultraviolet spectrum also showed a characteristic band at ~300 mμ with an absorptivity of ~18,900 l./mole cm. (isoöctane).

The reaction of this substance (I) with acidic 2,4-dinitrophenylhydrazine gave a 2,4-dinitrophenylhydrazone (2,4-DNP) of m.p. 235.6–236°; the latter was not depressed on 50:50 admixture with authentic benzaldehyde 2,4-dinitrophenylhydrazone.

The nitrone (2.1 g.) was reduced with excess lithium aluminum hydride in ether solution. This reduction gave a yield of dibenzylhydroxylamine of 1.3 g.; m.p. 123–124.5°. The melting point was not depressed by 50:50 admixture with authentic dibenzylhydroxylamine.

Reaction of N,N-Diethylhydroxylamine and *t*-Butyl Hydroperoxide.—*t*-Butyl hydroperoxide (0.062 mole; 94–99% material purified by vacuum distillation) was diluted with benzene and purified diethylhydroxylamine (0.0613 mole; $n^{25}D$ 1.4176) was added. The mixture was quickly brought to the 100 ml. mark in a volumetric flask and placed in the dark (~25°). The reaction was followed by periodic infrared analysis and the first analysis (15 min.) clearly showed the presence of the nitrone band (6.2 μ). [At ~60 min., the nitrone band showed an absorbance of ~0.29 (0.115 mm., corrected for some contribution from benzene). Anhydrous magnesium sulfate (~3 g.) was added directly to the reaction mixture at this point to remove

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[5] See ref. 1a. The e.m.r. spectrum consists of fifteen lines, three lines of equal intensity from the nitrogen nucleus, each of which is split into a quintet by the four α hydrogens. The relative intensity within each quintet is 1:4:6:4:1. The line splittings are A_H, 9.1 gauss, A_N, 15.6 gauss.

[6] Production of IV could occur by direct electron exchange. However, the formation of an intermediate quaternary ammonium salt (5) by displacement on the O—O bond of the hydroperoxide followed by homolytic cleavage of the N—O bond seems more consistent with the observations of other amine-peroxide systems, C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 590–595; C. Walling and N. Indicator, *J. Am. Chem. Soc.*, **80**, 5814 (1958). At any rate it seems certain that the initial step cannot result from thermal decomposition of the hydroperoxide.

[7] In the preparation of I the reaction was run at room temperature in the dark ($[RO_2H] \approx 0.25$ m./l. and $[RNH_2] \approx 0.20$ m./l.) where the nitrone band (6.31 μ) appeared early in the reaction and reached a maximum value consistent with the disappearance of peroxide. A subsequent heating period (50 hr. at 40–45°) produced only a small increase in the nitrone absorbance, and this was accompanied by a further decrease in the peroxide absorbance.

[8] J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

[9] C. Shramm, *Ber.*, **16**, 2184 (1883).

[10] We are indebted to W. W. Spooncer of these laboratories for supplying the purified material.

[11] Small water phase separated on standing.

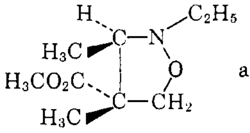
water as formed in the reaction.] The disappearance of the peroxide band at ~11.8 μ indicated that at least 90% of the peroxide had reacted in *72 hr.* After removal of 2 ml. for g.l.c. analyses, methyl methacrylate (10.2 g.; 0.1 mole) was added and the reaction mixture heated at ~60° for 17 hr. At the end of this time the 6.2-μ band had essentially disappeared, being replaced by the 6.1-μ carbon–carbon double bond stretch of methyl methacrylate. The mixture was concentrated by distillation and the concentrate fractionated through a micro-Vigreux column (see Table I).

TABLE I

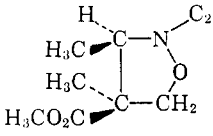
Fraction	Wt., g.	B.p., °C. (mm.)	$n^{22.5}D$	Isomer distribution (B:A) % of mixture
1	1.48	99–101/28	1.4378	80:20
2	5.57	101–102.5/28	1.4383	77:23
3	1.42	102/28	1.4392	63:36
4	0.29	60 ↓ /5	1.4414	37:58
Residue	.7			

Fractions 1–4 were analyzed by g.l.c. (85°, 10 p.s.i.g. N_2, 10-ft. Silicone SE-30) and found to consist of principally two isomers differing in retention time by ~3 min. under the stated conditions. We *presume* A and B to have the structures shown.[4]

The nuclear magnetic resonance spectra were determined for fraction 2 and for individual isomers A and B collected at the exit end of a g.l.c. column. The n.m.r. analysis[12] was consistent with geometrical isomers having the proposed structure (0 attachment to —CH_2—) and distribution; however, it was not possible to establish the identity of the individual isomers and the assignment of A to the higher boiling isomer is not certain.


A

and


B

An aliquot of fraction 2 was taken for analysis.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.6; H, 9.15; N, 7.52. Found: C, 57.6; H, 9.2; N, 7.8, 7.9 (Dumas).

The infrared spectrum of III shows a characteristic ester band at 5.72, strong absorption in the 8–9-μ region, and a characteristic set of moderately strong, sharp bands at 10.08, 10.57, 11.36, 12.10, and 13.18 μ.

An aliquot of another reaction mixture was converted to a 2,4-dinitrophenylhydrazone (m.p. 145–147°; ~85% yield).

Anal. Calcd. for $C_8H_8N_4O_4$: C, 42.9; H, 3.6; N, 25.0. Found: C, 43.0; H, 3.8; N, 24.6.

Mixture melting point with the higher melting modification of acetaldehyde 2,4-dinitrophenyl hydrazone (m.p. 167–168°) showed no depression.

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(12) We are indebted to our colleagues J. L. Jungnickel and C. A. Reilly for the determination and resolution of the n.m.r. spectra.

The Reaction of Ammonia with Acylated Disaccharides. I. Acetyl Derivatives of Cellobiose

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The reaction of methanolic ammonia with α-octa-O-acetylcellobiose is described. From the reaction were isolated cellobiose, N,N′-diacetylcellobiosylidenediamine, and a hepta-O-acetyl-N-acetylcellobiosylamine which is considered the alpha anomer of the product already described as hepta-O-acetyl-N-acetylcellobiosylamine. The acetyl derivative of N,N′-diacetylcellobiosylidenediamine was prepared and the influence of solvent upon the reaction studied is discussed.

Wohl's study[1] on ammonia degradation of acetylated D-gluconназваниеnitrile, introduced for the first time the so-called "aldose–diacetamides," derivatives which possessed two acetyl groups on carbon atom 1.

Later work on this subject, developed mainly by Brigl, Mühlschlegel, and Schinle[2] and Deulofeu and Deferrari[3–5] pointed out that these types of compounds could be obtained not only by degradation of acetylated nitriles, but by ammonolysis of partially or fully acetylated aldoses. In all cases, the principal product of the reaction was the corresponding "aldose–diamide," obtained in yields varying between 20 and 80%, depending both on the nature of the sugar and the substituents. An exception was found by Hockett and Chandler[6] and by Nieman and Hays[7] in the case of glucose acetates, which gave as a principal product N-acetyl-D-glucofuranosylamine.

In this paper we extended the knowledge of this reaction to the field of disaccharides. The nitrogenated products obtained through this reaction could be named, in a general manner, "aldobiose–amides" (or more correctly, N,N′-diacylaldobiosylidenediamines and N-acylaldobiosylamines), and this study would allow us to know the influence upon the course of reaction by the carbohydrate moiety glycosidically linked to carbon atom 4 of the reducing moiety of the disaccharide.

The first known attempt at degradation of acetylated disaccharides by ammonia was Zemplen's, who attempted to apply Wohl's reaction to octa-O-acetylcellobionic acid nitrile and obtained amorphous substances.[8]

Zemplen supposed he had obtained acetamido derivatives on carbon atom 1 which were not useful for his proposed studies and therefore did not continue his investigation.

Zechmeister and Toth[9] dissolved octa-O-acetylcellobiose in liquid ammonia and maintained the solution at 55° for forty-eight hours. From the products of the reaction they isolated an N-acetylcellobiosylamine (m.p. 246°; $[\alpha]^{20}D$ −20.3°, water) whose acetate had m.p. 196°; $[\alpha]^{20}D$ −8.4° (chloroform). Acetylation of the residual sirup led to the isolation of a fully acety-

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(1) A. Wohl, *Ber.*, **26**, 730 (1893).

(2) P. Brigl, H. Mühlschlegel, and R. Schinle, *ibid.*, **64**, 2921 (1931).

(3) V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

(4) J. O. Deferrari and V. Deulofeu, *ibid.*, **17**, 1093 (1952); **17**, 1097 (1952).

(5) J. O. Deferrari and V. Deulofeu, *ibid.*, **22**, 802 (1957).

(6) R. C. Hockett and L. R. Chandler, *J. Am. Chem. Soc.*, **66**, 957 (1944).

(7) C. Nieman and J. T. Hays, *ibid.*, **67**, 1302 (1945).

(8) G. Zemplen, *Ber.*, **59**, 1254 (1926).

(9) L. Zechmeister and G. Toth, *Ann.*, **525**, 14 (1936).