Reactions of Bicyclic Nitroxides Involving Reduction of the NO Group[1]

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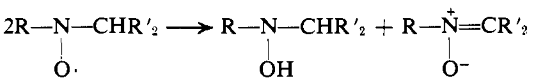
Abstract: The preparation of nortropane *N*-oxyl (8-azabicyclo[3.2.1]octane *N*-oxyl) and some homologs and derivatives is described. This radical oxidizes hydrogen peroxide and 2-propanol; labeling studies show that the bridgehead protons are not involved in these reactions. Nortropane *N*-oxyl dimerizes irreversibly in several solvents to give a product resulting from attack at a bridgehead position. In benzene at temperatures from 10 to 65°, the rate of this reaction is described by the equation $k_{\text{dec}} = 10^{10.9} \exp(-21{,}700 \pm 1800\ \text{cal}/RT)\ M^{-1}\ \text{sec}^{-1}$. The homolog, 9-azabicyclo[3.3.1]nonane *N*-oxyl, decays very much more slowly. In benzene at 30° this decay appears to be a first- rather than a second-order process.

In 1966 Dupeyre and Rassat[3] isolated a member of a new class of nitroxides in which the nitroxide nitrogen was joined to two bridgehead carbon atoms of a bicyclic structure. Radicals of this type containing α hydrogens are protected from the normal disproportion, which yields a hydroxylamine and a nitrone,[4,5] because the resulting double bond would appear at a bridgehead and would violate Bredt's rule.[6] In this paper we show that the bicyclic nitroxide nortropane *N*-oxyl nevertheless does decompose through this route, although the reaction is many orders of magnitude slower than for acyclic nitroxides, and the nitrone formed is extremely reactive. The homolog 9-azabicyclo[3.3.1]nonane *N*-oxyl decays at an even lower rate.



$$2\underset{\displaystyle \mathrm{O}\cdot}{\mathrm{R{-}N}}\mathrm{{-}CHR'_2} \longrightarrow \underset{\displaystyle \mathrm{OH}}{\mathrm{R{-}N}}\mathrm{{-}CHR'_2} + \mathrm{R{-}}\underset{\displaystyle \mathrm{O^-}}{\overset{+}{\mathrm{N}}}\mathrm{{=}CR'_2}$$

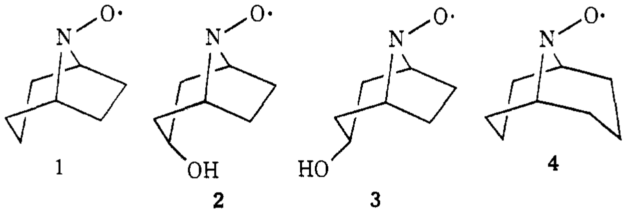
Other solution properties of nortropane *N*-oxyl demonstrate unusual reactivity in hydrogen abstractions from hydrogen peroxide and 2-propanol.

Results

Nortropane *N*-oxyl (**1**), nortropine *N*-oxyl (**2**), norpseudoptropine *N*-oxyl (**3**), and 9-azabicyclo[3.3.1]nonane *N*-oxyl (**4**) were prepared from the corresponding bicyclic amines, hydrogen peroxide, and phosphotungstic acid[3] (Chart I). Though the reactions proceeded readily, the products isolated were difficult to purify. Analytical samples of **1** and **4** were prepared as volatile, colored solids by lengthy procedures. Compounds **2** and **3** could not be sublimed, and crystallization gave products that were less pure by epr assay.

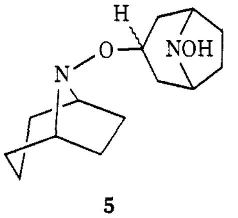
Crystalline samples of the nitroxides were stable for weeks at 25°, and **1** could be recovered from acidic and basic aqueous solutions.

Chart I



benzene 25°				
a_{N}	19.57 G	19.80	19.33	17.99
a_{H} (2 H)	5.3	5.6	4.8	*a*
a_{H} ($\geq$4 H)[b]	0.85	1.4	1.25	*a*
g	2.0065	2.0065	2.0066	2.0067

[a] No resolution even at −160° in isopentane. [b] Incompletely resolved splitting from four or more approximately equivalent hydrogens. Resolution increases along the series **1** < **2** < **3**.



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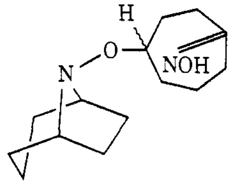

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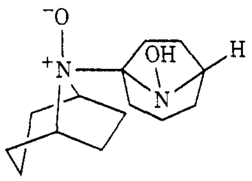

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Solutions of **1** in some organic solvents deposited a microcrystalline, colorless solid on standing. The compound could be isolated in 80% yield from a CCl_4 solution; other, dark products were also formed but these were not investigated. The crystalline product was shown by molecular weight determination to be a dimer of **1**, although spectral data were not sufficient to assign a structure. The dimer melted at 155° and decomposed to dark products on further heating. A unique proton in the nmr spectrum at δ 4.4 supported structures **5** or **6**. The latter was ruled out by the uv spectrum of the dimer. All attempts at reductive cleavage of the dimer led to oils, solids of unknown structure, or to nortropane. One unstable fragment may be 1-hydroxynortropane (see Experimental Section). Nortropine and norpseudotropine were synthesized

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[1] Issued as National Research Council of Canada No. 13421.

[2] National Research Council of Canada Postdoctorate Fellow, 1971–1973.

[3] R. M. Dupeyre and A. Rassat, *J. Amer. Chem. Soc.*, **88**, 3180 (1966).

[4] K. Adamic, D. F. Bowman, T. Gillan, and K. U. Ingold, *ibid.*, **93**, 902 (1971).

[5] R. Briere, Thesis, Grenoble, France, 1970.

[6] J. Bredt, *Justus Liebigs Ann. Chem.*, 437, 1 (1924); F. S. Fawcett, *Chem. Rev.*, 47, 219 (1950).

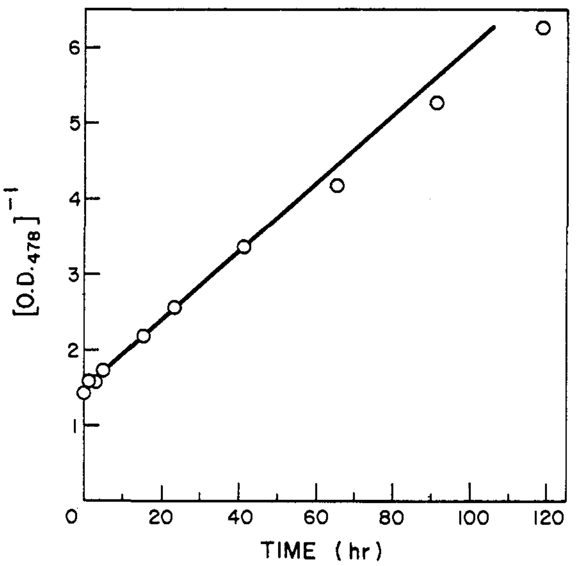
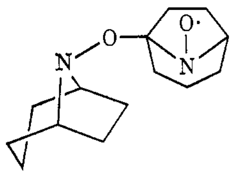


Figure 1. Decay of 0.64 M **1** in benzene at 30°.

in the anticipation that the dimer would be **5**. Comparisons of these compounds with the reduction mixtures by tlc or spectral means were inconclusive.

An X-ray structure determination[7] revealed that the dimer was represented by the unexpected structure **7**. A minor red product isolated from **1** and Ag_2O was shown[7] to be a related nitroxide **8** (Chart II). Since **8** exhibits a major splitting from only one hydrogen it must be concluded that the two hydrogens that produce major splittings in **1**, **2**, and **3** are in the bridgehead positions.

Chart II



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$a_N = 19.3$ G
a_H (1 H) = 7 G
a_H (many H)[a] = 0.6 G
g = 2.0072

[a] Poorly resolved splitting from (probably) ten hydrogens that are not all equivalent.

Irreversible Dimerization of 1. The rate constant for the coupling reaction of nortropane N-oxyl to give **7**

$$\mathbf{1} + \mathbf{1} \xrightarrow{k_{dec}} \mathbf{7}$$

was measured in benzene at temperatures from 10 to 65° by visible and by epr spectroscopy (see Figures 1 and 2 and Table I). The rate constant for the coupling reaction can be described by: $k_{dec} = 10^{10.9} \exp(-21{,}700 \pm 1800\ \text{cal}/RT)\ M^{-1}\ \text{sec}^{-1} = 1 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ at 25°. For comparison, the rate constant for the disproportionation of diethyl nitroxide in benzene is given by[4] $k_{dec}^{Et_2NO\cdot} = 10^{5.2} \exp(-1400 \pm 1000\ \text{cal}/RT)\ M^{-1}\ \text{sec}^{-1} = 1.36 \times 10^{4}\ M^{-1}\ \text{sec}^{-1}$ at 25°.

A single run in *tert*-amyl alcohol showed that the radical decayed initially with a rate constant k_{dec} of $10^{-5.3}\ M^{-1}\ \text{sec}^{-1}$ at 30°. The dimerization was observed to occur also in CCl_4, ether, hexane, and in the neat state by heating at 64° for 17 hr in a sealed tube.

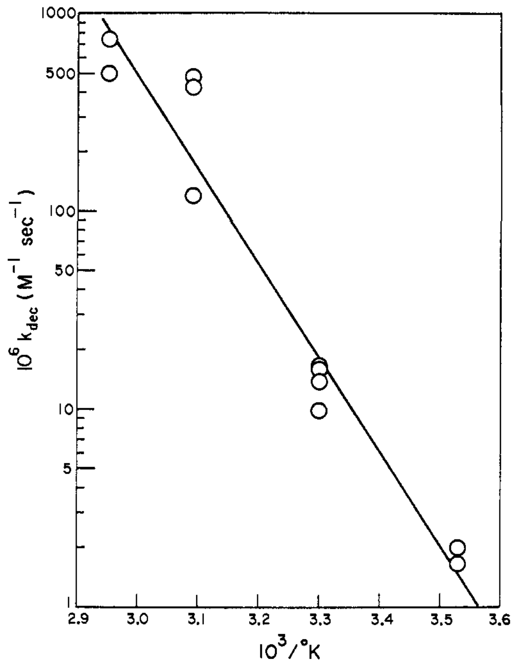


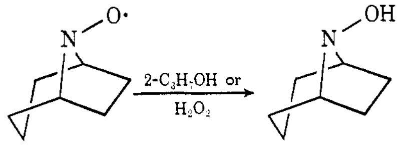
Figure 2. Arrhenius plot for the reaction 2 **1** → **7**.

Table I. Irreversible Dimerization of Nortropane N-Oxyl in Benzene

[1], M[a]	Temp, °C	$10^6 k_{dec}$, M^{-1} sec^{-1}	Method
0.53	10	1.66	Vis[b]
0.064	10	2.0	Vis
0.45	30	9.8	Vis
0.85	30	16	Vis
0.08	30	16	Vis
0.64	30	13.8	Vis
0.055	50	480	Epr
0.114	50	430	Epr
0.078	50	120	Vis
0.048	65	750	Epr
0.085	65	500	Epr

[a] Initial concentration. [b] At 478 nm in degassed quartz cell.

Reduction of 1 to N-Hydroxynortropane. The radical **1** is reduced to the corresponding hydroxylamine under a variety of conditions (see Experimental Section). Reduction of 0.08 M **1** in 2-propanol is complete after 5 hr reflux. There was essentially no deuterium incorporation into the bridgehead position of the product on reduction of **1** with 2-propanol-d_8.



1 1-H

It was more surprising to find that **1** (and **4**) readily oxidized concentrated, aqueous hydrogen peroxide at room temperature, since this reagent is also used for the synthesis of **1**, and oxidation of hydroxylamines by molecular O_2 is a common experience.[4] Reduction in H_2O_2–D_2O mixtures demonstrated again that bridge-

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(7) E. C. Gabe and G. D. Mendenhall, unpublished results.

Table II. Reduction of **1** in Deuterated Solvents

Reductant	[**1**], M^a	Methine:methylene^b
15 µl of 30% H_2O_2 + 100 µl of D_2O, 25°	0.76	Found 1.8:10 Expect^c 1.92:10
2-C_3D_7OD, 50°	0.68	Found 1.5:10 Expect^c 1.85:10

^{a} Initial concentration. ^{b} From integrated nmr spectrum of reaction products. ^{c} From ratios of **1**-H in D_2O and in 2-C_3H_7OD–$CDCl_3$, respectively (error 5%).

head protons are not affected (Table II). A singlet molecular oxygen trap, 2-methyl-2-pentene, was not oxidized by **1** and H_2O_2 to products expected from $^1O_2$.

Experimental Section

The following sequences gave the bicyclic amines we used to prepare the nitroxides. Tropine (Aldrich) → tropidine[8] (73%) → tropane (760 mm H_2, 25°, 5% Pd on C, CH_3OH, 75% yield) → nortropane[9] (40–71%). 3-Oxoglutaric acid (Fisher) → tropinone[10] (50%) → tropane[11] (*ca.* 100%). Tropinone → pseudotropine[12] (60%) → norpseudotropine[9] (65%). Tropine → nortropine[9,13] (30–40%). 9-Azabicyclo[3.3.1]nonane was obtained by reduction[11] of norpseudopelletierine[14] followed by oxidation.[9]

Nortropane *N*-Oxyl (1). A mixture of nortropane (1.92 g), water (15 ml), 35% hydrogen peroxide (3 ml, Baker reagent), and *ca.* 20 mg of phosphotungstic acid was heated rapidly to 40–50° and held at that temperature by occasional cooling until gas evolution ceased. The orange solution was saturated with salt and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated to a red gum (1.83 g) that crystallized on addition of 7 ml of hexanes. The yellow nodules were filtered after 1 hr at −18°, 0.37 g. The mother liquors were concentrated and recycled with water (7 ml), hydrogen peroxide (3 ml), and catalyst as before. Work-up gave 0.46 g of additional material (total yield 38%), phase change 74°, mp *ca.* 84–95°. An analytical sample was prepared by four wasteful (and not always successful) sublimations. The resulting product melted at 133.5–136° (phase change at 74°) and resembled *p*-benzoquinone in color and odor. *Anal.* Calcd for $C_7H_{12}NO$: C, 66.62; H, 9.59; N, 11.10; mol wt 126.18. Found: C, 66.39; H, 9.44; N, 10.91; mol wt, 133 (vapor pressure thermistor in benzene). Major *m/e* at 127, 111, 96, 82, 68, 54, and 44; ir (paraffin mull) 1330 (vs, probably due to NO group), 1285, 1160, 1035, 950, 840 cm^{-1}.

Nortropine[13] and norpseudotropine *N*-oxyls were prepared in the same manner and crystallized directly from the reaction mixture as stable insoluble yellow solids, mp 134–143° and 120–123°, respectively. Neither compound responded to purification attempts, though both displayed epr, ir (strong absorption in paraffin mull at 1336 and 1345 cm^{-1}, respectively), and mass spectra (major *m/e* 143, 141, 127, 126, 110, 98, 82, 68, 44) consistent with the assigned structures.

***N*-Hydroxynortropane.** This compound was isolated on reducing the nitroxide by (a) eluting it from silica gel (Davison Co.) with 10% ethanol in benzene, (b) refluxing a 0.087 *M* solution in 2-propanol for 5 hr (86% yield), (c) photolysis with λ >313 nm of a degassed solution 8 × 10^{-3} *M* in 2-propanol at 30° (86%), (d) reduction with PtO_2 in methanol and 760 mm H_2 (96%), and (e) from a 0.64 *M* aqueous slurry with 1 equiv of H_2O_2 (83% yield). Smaller amounts were isolated on refluxing the nitroxide in *tert*-butyl alcohol (39%) or in cyclohexane (23%) until the nitroxide had disappeared (epr assay). In all cases the product was isolated as a waxy solid, mp *ca.* 118° subl, by sublimation and identified by spectral methods or by conversion to **1**. The mass spectrum was virtually identical with that of **1**. Ir (paraffin mull) 3540 (OH), 3300 (s, OH bonded), 1335, 1200, 1080, 1040 cm^{-1}.

The hydrochloride was prepared in ethanol and crystallized from acetone, mp 205° dec. *Anal.* Calcd for $C_7H_{14}NOCl$: C, 51.37; H, 8.62; N, 8.56. Found: C, 51.21; H, 8.76; N, 8.49.

***N*-Hydroxynortropine.** This compound was prepared by catalytic (5% Pt on C) reduction of crude **2** in 95% ethanol and was purified by crystallization (ethanol–ether) of the hydrochloride, mp >200° dec. *Anal.* Calcd for $C_7H_{13}NO_2Cl$: C, 46.80; H, 7.86; N, 7.80. Found: C, 46.69; H, 8.05; N, 7.61.

Attempt to Trap Singlet Molecular Oxygen from 1 and H_2O_2. A mixture of **1** (0.0277 g), methanol (400 µl), 2-methyl-2-pentene (50 µl), and 30% hydrogen peroxide (50 µl) was allowed to stand 2 hr and then reduced with 0.2 g of triphenylphosphine. Analysis by vpc, assuming the two alcohols derived from singlet oxygen[15] have the same detector response as 1-hexen-3-ol, indicated an upper limit of 2% yield of alcohols (based on **1**). An attempt in aqueous solution with the olefin as a separate layer likewise gave no detectable alcohol.

***N*-(*N'*-Hydroxynortropan)-1'-yl Nortropane *N*-Oxide (7).** A solution of **1** (0.06330 g) in 0.50 ml of CCl_4 (1.0 *M*) was allowed to stand 12 days at 25°. The white precipitate was filtered off and dried 2 hr (0.1 mm): 0.0506 g (80%) of white nodules; mp 156–156.5° dec; ir (Nujol) 3500–2300 (OH), 1330, 1250, 1170, 1070, 1045, 1020, 985, 925, 880, 800, 700 cm^{-1}; major *m/e* at 127, 125, 111, 97, 82, 68, 55, and 44; mol wt (in benzene) 257 (calcd for dimer, 252). A 0.0012 *M* aqueous solution showed only end absorption (OD 0.20 at 217 nm). The same concentration of cyclohexanone oxime showed end absorption but with OD = 0.20 at 248 nm.

The hydrochloride was prepared in water and crystallized from ethanol–ether, mp 180–183° dec. *Anal.* Calcd for $C_{14}H_{25}N_2O_2Cl$: C, 58.22; H, 8.73; N. 9.70. Found: C, 58.09; H, 8.90; N, 9.54.

Reduction of 7. A solution of **7** (0.94 g, 3.73 mmol) in 10 ml of 95% ethanol containing 0.30 g of 5% Pd/C catalyst (Engelhard Industries) was stirred under 760 mm of hydrogen at 60–70°. In 5 hr 170 ml (6.95 mmol) of H_2 was absorbed. The solution was filtered and concentrated to an oil that crystallized, 0.96 g. The colorless product was triturated with hexanes (10 ml), filtered, washed with hexanes, and pumped dry, 0.15 g. Crystallization from benzene and sublimation at 1 mm gave sticky crystals: mp 113–116°; ir (paraffin mull) 3250, 3500–2200 (broad), 1340, 1190, 1120, 1040 (strong), 930, and 910 cm^{-1}; nmr ($CDCl_3$) δ 1.20–2.10 (m, area 160), 3.12 and 3.33 (partly resolved, broad singlets, area 45); mass spectrum (major *m/e*) 127 (parent), 109–112, 99, 98, 84, 70, 56. A 0.015 *M* (based on mol wt 127) solution in CCl_4 (1-mm path) showed ν_{max} 3600 (strong, OH), 3400 (vw, NH?) and 3140 cm^{-1} (broad, H-bonded). The ir and nmr spectra did not match those of the bicyclic amines we prepared. Attempts to further purify this solid gave glassy materials with strong absorption at 1695 cm^{-1}.

The original filtrate was concentrated, taken up into CCl_4 (1 ml), filtered, and reconcentrated. Distillation by the bulb-to-bulb technique at 1 mm gave nortropane (0.20 g, 1.82 mmol), identified by ir and by conversion to **1**.

Other attempts to reduce **7** with $LiAlH_4$ (Et_2O or THF), PtO_2/H_2 (HOAc or EtOH), or photolytically (λ >313 nm) in 2-propanol gave oils or unidentified products.

***N*-(1'-Nortropanoxy)nortropane *N'*-Oxyl (8).** A mixture of nortropane *N*-oxyl (0.75 g) in hexane (70 ml) was stirred 24 hr with silver oxide (0.15 g). (The latter was prepared by precipitation from silver nitrate with barium hydroxide, washed well, and dried 48 hr at 120°.) The mixture was filtered, concentrated under reduced pressure, and sublimed. A large residue of **7** remained. The sublimate consisted initially of **1** which slowly took on a diseased appearance from small red crystals of **8**. These were separated mechanically and resublimed, mp 99–102°, 2% yield. The structure was determined by X-ray crystallography. This preparation failed with impure **1** or with old samples of silver oxide. Attempts to prepare **8** by stirring solutions of **7** (crude or recrystallized) and silver oxide followed by sublimation were not successful. Irradiation of 0.00005 *M* **7** in benzene with λ >313 nm gave 0.00002

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[8] A. Ladenberg, *Justus Liebigs Ann. Chem.*, **217**, 74 (1883).

[9] Procedure of A. T. Bottini, C. A. Grole, E. Schumacher, and J. Zergenyi, *Helv. Chim. Acta*, **49**, 2522 (1961). The filtered reaction mixture was boiled several hours with dilute sulfuric acid to hydrolyze the *N*-formyl derivative.

[10] G. I. Bazilevskaya, D. V. Gura, M. S. Barnova, K. M. Dyumaev, I. K. Sarycheva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **28**, 1097 (1958); *Chem. Abstr.*, **52**, 18486 (1958). The compound was also purchased from Aldrich Chemical Co.

[11] Procedure from Sandoz Ltd., *Neth. Appl.*, **6**, 500,007 (1965); *Chem. Abstr.*, **64**, 2066 (1966).

[12] A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.*, **74**, 5566 (1952).

[13] E. G. Rozantsev and V. P. Ivanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 6, 1416 (1970).

[14] A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 816.

[15] C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968).

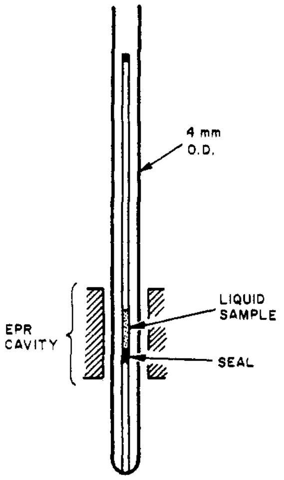


Figure 3. Sample tube for epr spectrometer.

M of a nitroxide but the fine structure of the spectrum did not match that of **8**. Oxidation of **7** in benzene with Ag_2O or $(t\text{-}C_4H_9ON)_2/h\nu$ gave at least two radicals (triplets) neither identical with **8**.

9-Azabicyclo[3.3.1]nonane *N*-Oxyl (4). This radical was prepared in the same manner as **1** and was isolated in low yield as deep red volatile crystals with a musty odor. The product was recrystallized from isopentane at −20° and sublimed. An analytical sample was prepared by passing an ether solution through a short column of alumina followed by sublimation: phase change 53° and *ca.* 70°, mp 129–133°; major *m/e* 141, 140, 125, 122, 96, 82, 67, 55, 43. *Anal.* Calcd for $C_8H_{14}NO$: C, 68.53; H, 10.07; N, 9.99. Found: C, 68.25; H, 10.19; N, 9.82.

2,2,6,6-Tetramethylpiperidine *N*-oxyl was prepared from the amine (Eastman) in the same way; mp 40–41° and 38–39° for two preparations (lit.[16] mp 37–38.1°).

The nmr spectral parameters listed in Table III were obtained on a Varian HA 100 nmr spectrometer.

Table III. Nmr Data for Tropane and Derivatives[a]

Compd	$-CH_2-$	Bridgehead CH	Methine	CH_3	OH or NH
Tropane	1.2–2.0	3.1		2.2	
Tropine	1.5–2.2	3.1	4.0 tripl.	2.2	2.9
Pseudotropine	1.4–2.1	3.2	3.9	2.3	3.0
Nortropane	1.3–2.0	3.5			2.3
Nortropine	1.4–2.4	3.5	4.0		2.2 sh
Norpseudotropine	1.2–2.1	3.5	3.9 mlt.		2.6
1-H	1.1–2.2	3.55			8.6
7	0.7–2.2	3.6	4.4		11.2
9-Azabicyclo-[3.3.1]nonane	1.4–2.1	3.7			3.1 (?)

[a] Ppm relative to TMS in $CDCl_3$.

Stability of 1 in Acid and Base. A solution of **1** (0.102 g) in 10 ml of water was acidified with 5 drops of concentrated hydrochloric acid. The color of the solution lightened to yellow. After 5 min, 0.1 *M* sodium hydroxide was added to pH 10, and the orange solution was allowed to stand 5 min. After saturating with NaCl, the radical was extracted with methylene chloride. Evaporation of the organic solvent left 0.083 g (81% recovery) of **1** identified by its ir spectrum.

General. The epr instrument and signal processing accessories were the same as described previously.[4] Uv-visible spectra were recorded on a Cary 15 instrument. Infrared spectra were recorded with a Beckman IR-10. Melting points were determined with a hot stage (Kofler) and microscope and are uncorrected.

The determination of reaction rates for concentrated solutions of radicals poses special problems because the signal shape changes as the reaction progresses (peak heights are not proportional to concentration). For very slow reactions instrument stability becomes difficult. We found that reasonable data could be obtained if the epr instrument was equilibrated overnight at ambient temperature.

Sample tubes were prepared as follows. An open-ended melting point capillary was sealed about 2 cm from one end, weighted, and flushed with argon. A sample of **1** was loaded from the long end in the normal manner and its weight determined. Argon-flushed solvent (8–25 μl) was introduced (microliter syringe) and the lower part of the tube was frozen by brief immersion in liquid nitrogen. After flushing the tube with argon the tube was sealed at the top end. A 4-mm OD tube was sealed off and the lower part of the capillary was broken off at a point such that the liquid was centered in the cavity when the capillary rested in the larger tube (Figure 3). The 4-mm tube was then sealed off, wrapped in foil, and immersed in a constant-temperature bath.

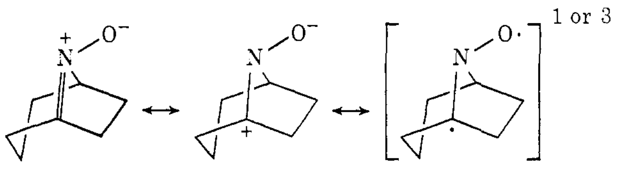
Samples for visible spectroscopy were prepared in 1-cm and 0.1-cm quartz cells with two extra arms, one for attachment to a vacuum line and the second for holding the solution during three freeze–thaw cycles. The arm leading to the vacuum line was sealed off and the apparatus was immersed in a thermostated bath. The optical density was recorded at 478 nm and 25° at intervals.

Discussion

A large number of mechanisms and transition states can be proposed for the conversion of **1** into **7**. They resolve themselves into an initial step in which the bridgehead proton is lost, and a coupling step in which the resulting fragment combines with another bicyclic residue (either a second nitroxide or the hydroxylamine derived from it) ultimately to give the dimeric product. There is no direct evidence to favor anything but a simple attack of one molecule of **1** on a second in the initial step, though concerted or more elaborate routes are not ruled out (*vide infra*).

$$1 + 1 \xrightarrow{\text{slow}} \text{1-H} + 9$$

$$9 \xrightarrow[\text{fast}]{(1\text{ or }1\text{-H})} 7$$



9

It is really rather surprising that coupling involves the bridgehead position. Although it is a tertiary C–H bond that is broken while all the other hydrogens are secondary, to a first approximation it is not expected to be weakened appreciably by the nitroxide group since the orbital containing the unpaired electron and this C–H bond are nearly orthogonal.

The product **8** is formally derived from **7** by a Meisenheimer rearrangement followed by oxidation, but we were unable to make it from **7** (crude or purified) and its origin remains uncertain.

The enhanced reactivity of **9** compared with ordinary nitrones is clearly shown by the fact that **1** (10^{-4} *M*) was inert toward two nitrones (0.1 *M*) commonly used as spin trapping agents.[17] The addition of nitroxides to nitrones has been proposed previously[4,18] and so the absence of reaction between **1** and these compounds is a little surprising.

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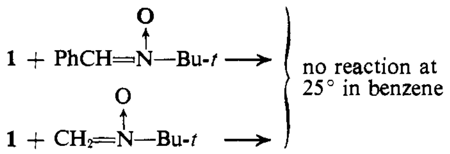
(16) E. G. Rozantsev, "Free Nitroxyl Radicals," (Engl. Trans.), Plenum Press, New York, N. Y., 1970, p 217.

(17) E. G. Janzen, *Accounts Chem. Res.*, **4**, 31 (1971), and references therein.

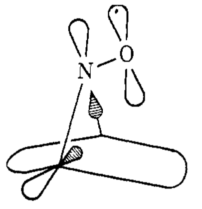
(18) C. M. Camaggi, R. J. Holman, and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 2*, 501 (1972).



$$\left.\begin{array}{l} \mathbf{1} + PhCH{=}\overset{\overset{\displaystyle O}{\uparrow}}{N}{-}Bu\text{-}t \longrightarrow \\ \mathbf{1} + CH_2{=}\overset{\overset{\displaystyle O}{\uparrow}}{N}{-}Bu\text{-}t \longrightarrow \end{array}\right\} \text{no reaction at } 25° \text{ in benzene}$$

A striking result is the great stability of **4** compared with **1**. This was first noted during its synthesis when solutions in several solvents did not form a colorless precipitate as did **1**, nor did an involatile residue of dimer remain when **4** was sublimed. A solid sample of **4** was heated for 17 hr at 64°. It underwent no change in physical appearance nor were any products formed that could be detected by thin-layer chromatography. A 0.62 *M* solution of **4** in 16 μl of CCl_4 was 44% decomposed on heating to 50° for 12 days. Thin-layer chromatography showed, in addition to undecomposed **4**, a streak extending from the origin. (At 25° a 1 *M* solution of **1** in CCl_4 was converted to **7** in 80% yield in this length of time; see Experimental Section.) The initial rate of decay of **4** in benzene at 30° is very much slower than that of **1** and the decay appears to be a first- rather than a second-order process (see Figure 4).

The difference in stability of **1** and **4** is puzzling because it is in a direction opposite to that expected from the relative stabilities of related bicyclic carbon radicals,[19] carbenium ions,[19] and compounds in which a double bond is attached to a bridgehead position.[20] In general, as the ring size decreases more energy is required to form such species. However, if the stabilizing overlap in the intermediate occurs in the "backside" orbitals of the bridgehead position and the nitroxide group as shown in the shaded portions of **10**,



10

we can see qualitatively that an increase in ring size from **1** to **4** will actually make this overlap less favorable and as a result the rate of abstraction will decrease.

Equilibrium studies of **1** and **4** with di-*tert*-butylketoxime and di-*tert*-butyliminoxy[21] indicate that the free energy of the reaction **1** + **4**-H → **1**-H + **4** is about 800 cal/mol in benzene at 25°. It is possible that the greater stability of **4** merely reflects the weaker OH bond strength of **4**-H, though if the respective abstractions proceed with the same preexponential factor the rate constant difference would be only, $\exp(800/RT) = 3.8$ at 30°.

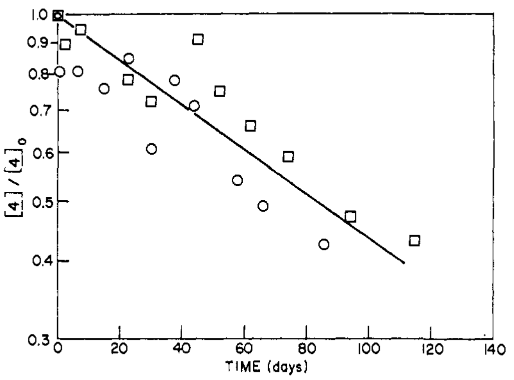
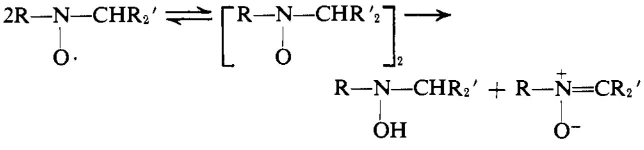


Figure 4. Decay of **4** in benzene at 30°. Initial concentrations: (○) 2.95 *M*; (□) 0.32 *M*.



$$2R{-}\underset{\displaystyle O\cdot}{\underset{|}{N}}{-}CHR_2' \rightleftharpoons \left[R{-}\underset{\displaystyle O}{\underset{|}{N}}{-}CHR'_2\right]_2 \longrightarrow R{-}\underset{\displaystyle OH}{\underset{|}{N}}{-}CHR_2' + R{-}\underset{\displaystyle O^-}{\underset{|}{\overset{+}{N}}}{=}CR_2'$$

We have previously proposed that the disproportionation of dialkyl nitroxides involves the intermediacy of a reversibly formed dimer and its irreversible decomposition by an intramolecular hydrogen transfer.[4] The irreversible dimerization of **1** may involve a similar intermediate. If it does, then **1** might be expected to be slightly less stable than **4** because the equilibrium constants (in isopentane) favor the dimerization of **1** by a small amount ($K_1/K_4 = 0.2$ at 25° in isopentane). Still another factor influencing the relative stability of **1** and **4** is suggested by Nelsen and Hintz's[22] measurements of the electrode potentials for a series of caged amines. Their results agreed with previous theoretical work[23] which indicated that special stability was achieved in those cases where a C–C bond is parallel with the axis of the orbital from which the electron is removed. However, this trend is not apparent in bridgehead carbon radicals and cations,[19] and whether our case resembles the nitrogen rather than the carbon analog is uncertain. To the extent that C–C delocalization does occur, it will stabilize the intermediate from **1** (*i.e.*, **9**) which has the C_5–C_6 bond in a colinear arrangement with the bridgehead orbital, but would not contribute in the intermediate from **4**, where no bonds are suitably orientated for this sort of overlap.

A decision as to which factor is most responsible for the differences between **1** and **4** is difficult in the absence of additional data with other nitroxides. The synthesis and purification of these radicals unfortunately are not easy, due to their ease of reduction and dimerization and to the similar physical properties of the related amine and hydroxylamine, which may replace the radical in the solid lattice as impurities.[24]

While this work was in progress, improved syntheses[25–27] of several bicyclic amines and their derivatives were reported. Further studies will probably benefit from these procedures.

Reduction of 1 in H_2O_2, 2-Propanol, and Other Solvents. The reaction of hydrogen peroxide with

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[19] See *e.g.*, C. Rüchart, *Angew. Chem.*, **82**, 845 (1970).

[20] For a recent summary, see J. R. Wiseman and J. A. Chang, *J. Amer. Chem. Soc.*, **94**, 8627 (1972).

[21] L. R. Mahoney, G. D. Mendenhall, and K. U. Ingold, unpublished work.

[22] S. F. Nelsen and P. J. Hintz, *J. Amer. Chem. Soc.*, **94**, 7114 (1972).

[23] For leading references, see ref 22.

[24] Inclusion complexes of nitroxides with paraffins have been reported: ref 16 and I. A. Prokop'eva, V. D. Galyaminskikh, A. Abakumov, R. O. Matevosyan, and A. K. Chirkov, *Dokl. Chem.*, 204, 433 (1972).

[25] J. W. Bastalile, J. D. Hobson, and W. D. Riddell, *J. Chem. Soc., Perkin Trans. 1*, 2205 (1972).

[26] G. C. Tustin, C. E. Monken, and W. H. Okamura, *J. Amer. Chem. Soc.*, **94**, 5112 (1972).

[27] W. B. Motherwell and J. S. Roberts, *Tetrahedron Lett.*, 4287 (1972).

1 (and **4**) is surprisingly rapid if it is a simple radical–molecule reaction, since the process

$$\mathbf{1} + H_2O_2 \longrightarrow \mathbf{1}\text{-H} + HOO\cdot$$

is endothermic by about 13 kcal/mol.[28] It therefore seemed possible that the oxidation of H_2O_2 involved ionic species present in equilibrium with the parent nitroxide. In view of the obvious possibility that the

$$\mathbf{1} + \mathbf{1} \rightleftharpoons \mathbf{1}^{+}\mathbf{1}^{-}$$

$$\mathbf{1}^{+} + H_2O_2 \longrightarrow \mathbf{1}\text{-H} + H^{+} + O_2$$

dimerization of **1** also involved ionic intermediates, this mechanism was tested in two ways. In the first place, direct measurement on the conductivity of **1** in acetonitrile (0.08 *M*) and benzene (0.07 *M*) did not reveal the presence of ions. Secondly, it is known that ionic oxidizing agents and hydrogen peroxide can give rise to singlet molecular oxygen.[15] However, attempts to trap singlet oxygen in the **1**–H_2O_2 reaction with 2-methyl-2-pentene were not successful.[30]

Reduction of **1** with 2-propanol-d_8 or with H_2O_2–D_2O mixtures led to insignificant deuterium uptake into the bridgehead positions of **1**-H (Table II). While these observations are consistent with either an ionic or a radical pathway for these reactions, it seems likely that neither proceeds through the intermediate **9** proposed to explain the irreversible dimerization. The kinetics of both reactions did not appear to be simple.

Although we isolated **1**-H from **1** in refluxing *tert*-butyl alcohol and cyclohexane, the yields were low and we suspect rather than solvent H-abstraction a process such as the following

$$2(\mathbf{1}) \longrightarrow \mathbf{7}$$

$$\begin{array}{l} \mathbf{7} + \mathbf{1} \rightleftharpoons \mathbf{1}\text{-H} + \text{nitroxide from } \mathbf{7} \\ \qquad\qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\quad \text{decomposition} \\ \qquad\qquad\qquad\qquad \text{products} \end{array}$$

This reaction does not occur at lower temperatures because strong intramolecular H-bonding in **7** shifts the equilibrium to the left.

The mechanism of photoreduction of **1** in 2-propanol is also ambiguous. We cannot distinguish between an excited state of **1** and radicals, or excited states, derived from solvent (or from solvent oxidation products, *e.g.*, acetone) as the reactive intermediates.[31]

Conclusion

The behavior of two bicyclic nitroxides indicates that their reactivity is considerably greater than that of more hindered derivatives such as di-*tert*-butyl nitroxide. The differences between the azaoctane **1** and azanonane **4** toward dimerization are interesting, and we suggest that these are due to several factors, (a) the different OH bond strengths of **1**-H and **4**-H, (b) a lower concentration in **4** of the reversible dimer, which may be an intermediate in the irreversible dimerization, and (c) different degrees of overlap of the bridgehead C–H orbital with other orbitals in the radical.

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(28) Taking D[**1**-H] = 77 kcal/mol[21] and D[HOO–H] = 90 kcal/mol.[29]

(29) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).

(30) The significance of this experiment may be limited by potential quenching of any singlet oxygen produced by **1** or **1**-H.

(31) The photoreduction of a hindered nitroxide has been reported: J. F. W. Keana, R. J. Dinerstein, and F. Baitis, *J. Org. Chem.*, **36**, 209 (1971).

Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. XI. Aminium Radicals[1]

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Contribution from the Division of Chemistry, National Research Council of Canada, Ottawa, Canada. *Received February 20, 1973*

Abstract: The bimolecular self-reactions of two aminium radicals have been studied by kinetic epr spectroscopy. For dimethylaminium in 0.95 *M* H_2SO_4–CF_3COOH the rate constant for decay is given by $2k_t = 10^{9.5} \exp(-5000 \pm 1500\ \text{cal}/RT)\ M^{-1}\ \text{sec}^{-1}$ and for 2,2,6,6-tetramethylpiperidinium in CF_3COOH by $2k_t = 10^{9.8} \exp(-7600 \pm 1000\ \text{cal}/RT)\ M^{-1}\ \text{sec}^{-1}$. For both radicals $2k_t$ is independent of solvent viscosity (up to 20 cP) but decreases by about one order of magnitude on changing the acidity of the solvent from an H_0 value of -3 to a value of -8. This is attributed to a decrease in the activity coefficients of the radicals. Various mechanistic possibilities are considered including hydrogen atom transfer from alkyl to nitrogen, $2R_2NH\cdot^{+} \rightarrow R_2NH_2^{+} + R(R_{-H})NH^{+}$, and from nitrogen to nitrogen, $2R_2NH\cdot^{+} \rightarrow R_2NH_2^{+} + R_2N^{+}$.

The exceptionally high selectivity obtainable in the radical-chain chlorination of organic compounds with *N*-chloramines[3–5] has generated great interest in the reactions of these radicals. However, a rotating sector study[6] of the photochemically ini-

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(1) Issued as National Research Council of Canada No. 13422. Part X: J. R. Roberts and K. U. Ingold, *J. Amer. Chem. Soc.*, **95**, 3228 (1973).

(2) National Research Council of Canada Postdoctorate Fellow, 1972–1973.

(3) F. Minisci, R. Galli, A. Galli, and R. Bernardi, *Tetrahedron Lett.*, 2207 (1967); F. Minisci, R. Galli, and R. Bernardi, *Chem. Commun.*, 903 (1967); *Chim. Ind.* (*Milan*), **49**, 594 (1967); *J. Chem. Soc.*, 324 (1968); F. Minisci, R. Galli, R. Bernardi, and M. Perchinumno, *Chim. Ind.* (*Milan*), **50**, 453 (1968); F. Minisci, G. P. Gardini, and F. Bertini, *Can. J. Chem.*, **48**, 544 (1970).

(4) J. Spanswick and K. U. Ingold, *Can. J. Chem.*, **48**, 546 (1970).

(5) N. C. Deno, W. E. Billups, R. Fishbein, C. Pierson, R. Whalen, and J. C. Wyckoff, *J. Amer. Chem. Soc.*, **93**, 438 (1971); N. C. Deno, R. Fishbein, and J. C. Wyckoff, *ibid.*, **93**, 2065 (1971); N. C. Deno, *Methods Free-Radical Chem.*, **3**, 135 (1972).

(6) J. Spanswick and K. U. Ingold, *Can. J. Chem.*, **48**, 554 (1970).