Oxidation and Mass Spectra of 4,4-Dimethyloxazolidine-*N*-oxyl (Doxyl) Derivatives of Ketones

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4,4-Dimethyloxazolidine-*N*-oxyls (doxyls), the very useful nitroxide spin labels, can be reconverted rapidly and efficiently to their parent ketones with nitrogen dioxide (conveniently as contained in commercial nitric oxide) in ethanol at room temperature. This reaction is interpreted as involving initial oxidation to give an oxoammonium salt, *e.g.*, **5** from **1**, followed by fragmentation to an oxonium ion, *e.g.*, **6**, and cleavage to ketone. The mass spectra of several doxyls and their precursor oxazolidines have been studied. The latter show a fragmentation pattern like that of ethylene ketals. The more interesting mass spectra of the doxyls can be interpreted on the basis of formation of the same molecular ion, *e.g.*, **5**, which results from chemical oxidation. This leads in a major fragmentation mode to protonated parent ketone as the base peak. Deuterium-labeled substrates and high-resolution identification of ion formulas were used to gain evidence for this pathway as well as for several other modes of breakdown of the oxoammonium molecular ions.

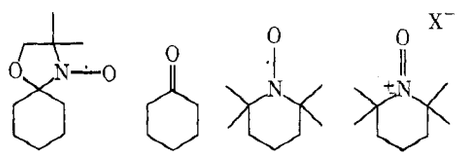
4,4-Dimethyloxazolidine-*N*-oxyl (doxyl) derivatives of ketones are among the more useful of the stable nitroxide free radicals which have recently gained prominence as spin labels. Since the first report[1] of their preparation in 1967, doxyls have been extensively used in the study of biological membranes and membrane models.[2-4] However, very little of the chemistry of these substances has been investigated.[5] In the course of another study[6] we discovered a rapid, efficient method for the reconversion of doxyl derivatives to the parent ketones.[7] This reaction and an analysis of the mass spectra of doxyls, which display a fragmentation pattern reminiscent of the doxyl → ketone conversion, are the subjects of this paper.

Reaction of Doxyls with Chemical Oxidizing Agents. If commercial nitric oxide is bubbled through an ethanol solution of doxyl 1 at room temperature for 5 min, cyclohexanone (**2**) is produced in 95% yield. The necessary reagent for this reaction is actually nitrogen dioxide, because no reaction occurs when the commercial NO is first bubbled through base to remove NO_2. Absolute ethanol is superior to the other solvents tried. The reaction, particularly in nonpolar solvents, is a visual delight: the initial orange-colored solution of nitroxide turns dark, then green or blue, and finally chartreuse.

Table I lists the doxyls and conditions which have been used in this reaction. The ketone is the only isolable product aside from an intractable, tarry residue. The fate of the heterocyclic portion of the nitroxides remains obscure. An extensive gc search for other products revealed only a few very weak, transient, unidentified peaks. Because isobutene is a possible product of this reaction, attempts were made, using gc, to determine whether it would have been detected if formed. Small added amounts (<1 equiv) of isobutene were not detectable, but larger amounts were, suggesting that isobutene, if formed, might itself have reacted further.[8]

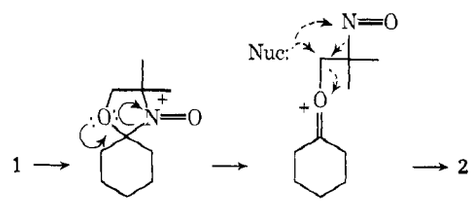
In the absence of any information regarding what happened to the heterocyclic moiety, assignment of a mechanism to the reaction of NO_2 with doxyls must remain incomplete in detail and tentative. However, a well-documented reaction[9-11] of other types of nitroxides with oxidizing agents to form oxoammonium salts suggested that analogous removal of an electron might be the first step in the conversion of doxyl to ketone. Typical examples of this type of oxidation are the conversions of nitroxide **3**[12] to **4a**, **4b**, or **4c** by chlorine,[9] bromine,[10] or $SbCl_4$,[11] respectively.

If such electron removal occurred with a doxyl, *e.g.*, **1**, to give **5**, fragmentation to oxonium ion **6** could ensue as a consequence of the unshared electrons of the ethereal oxygen, as shown in Scheme I. Elucidation of the details of the decomposition of **6** would depend on knowledge of the products from the doxyl moiety, but the fact that the reaction proceeds more cleanly in ethanol than in cyclohexane is consistent with the kind of nucleophilic attack suggested in **6** → **2** in Scheme I.



1 2 3 4a, X = Cl; b, X = Br; c, X = $SbCl_6$; d, X = NO_3

Scheme I



5 6

Evidence consistent with this hypothesis was obtained from treatment of nitroxide **3** with NO_2, which afforded 93% of oxoammonium nitrate **4d**. Treatment of doxyl **1** with chlorine led to formation of **2**,[13] plus 2-chlorocyclohexanone and a small amount of blue oil which eventually was assigned tentatively the intriguing structure **7**.

Blue oil **7** crystallized at low temperatures to a white solid which regenerated the blue oil upon melting. This behavior, plus its spectral properties (*e.g.*, ir 7.93 and 8.85 μ; uv max (EtOH) 295 nm) clearly suggested that it was a nitroso compound in equilibrium with its dimer. The substance was extremely difficult to characterize, however, owing to its instability even, for example, in solutions prepared for determination of its nmr spectrum.

Accordingly the nitroso compound was oxidized with *m*-chloroperbenzoic acid to the corresponding nitro compound **8**. This more tractable substance gave a clean nmr spectrum [δ 1.63 (s, 6), 1.6–2.3 (m, 6), 4.07 (s, 2), and 4.1–4.7 (m, 2)], and had a mass spectrum with an M^+ ion indicating that the compound contained three chlorine atoms. Structure **8** (stereochemistry uncertain) is the only one we have been able to formulate consistent with these data.[14]

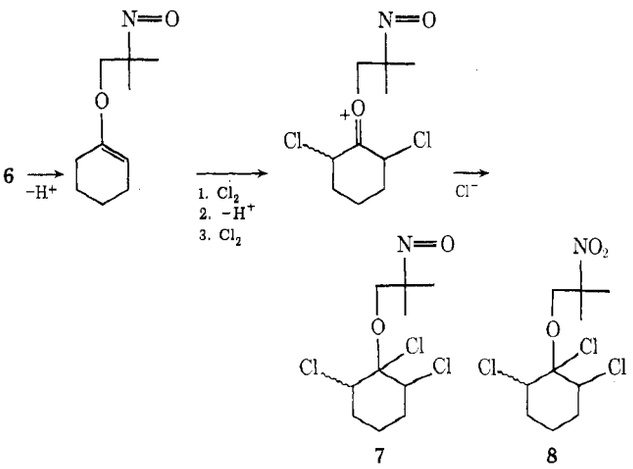
Table I
Reaction of Doxyls with Commercial Nitric Oxide[a]

Doxyl derivative of	Registry no.	Ketone Yield,[b] %	Ketone Solvent	Ketone Registry no.	Gc reference compd
Cyclohexanone[c]	16302-61-7	48	Benzene	108-94-1	Dodecane
		62	CCl_4		Dodecane
		66	Cyclohexane		Dodecane
		95	Absolute ethanol		Dodecane
2-Methylcyclohexanone[d]	35328-05-3	81	Cyclohexane	583-60-8	2,4-Dichlorotoluene
		100	Absolute ethanol		2,4-Dichlorotoluene
Cycloheptanone[d]	35328-03-1	93	Absolute ethanol	502-42-1	Tetradecane
Heptan-2-one[c]	16263-51-7	74	Cyclohexane	110-43-0	Tetradecane
Cholestan-3-one[c]	18353-76-9	68[e]	Cyclohexane	566-88-1	
		85[e]	Absolute ethanol		

[a] Room temperature, 5 min. [b] Determined by gc as described in the Experimental Section, unless otherwise noted. [c] Reported in ref 1. [d] New compound; see Experimental Section. [e] Yield of isolated, recrystallized ketone with mp 127–130°.

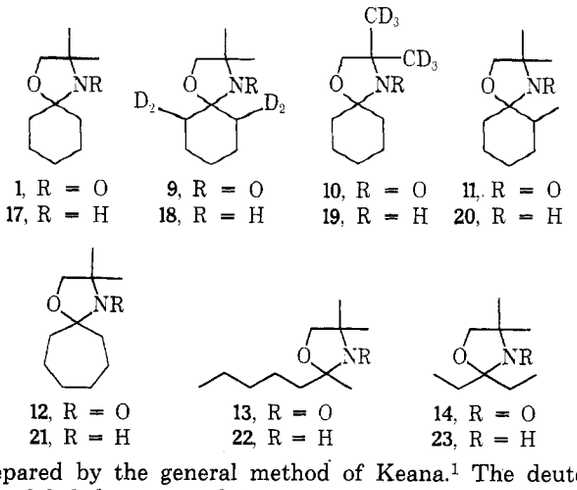
The precursor **7** could arise through the sequence shown in Scheme II, and its isolation is consistent with the proposed mechanism.

Scheme II



Mass Spectra of Doxyls. During attempts to gain information about possible intermediates in the conversion **1** → **2** by gc–mass spectral examination of reaction mixtures, the fragmentation patterns of the nitroxides themselves were determined, and these proved to be of sufficient interest to deserve careful analysis. Mass spectra of doxyls have not previously been investigated, although those of a few other nitroxides have been examined.[15-18]

In the present work, the mass spectra of doxyl derivatives **1** and **9–14** were studied. All of these substances were



prepared by the general method of Keana.[1] The deuterium-labeled compound **9** was prepared from cyclohexanone-*2,2,6,6-d*$_4$. The heterocyclically labeled **10** was made by the sequence shown in Scheme III, involving a Strecker synthesis[19] of amino acid **15** from acetone-d_6 and subsequent reduction of its trimethylsilyl derivative with lithium aluminum hydride[20] to produce aminopropanol **16**.

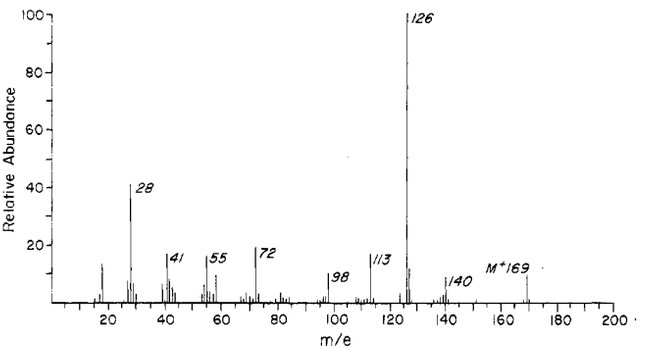
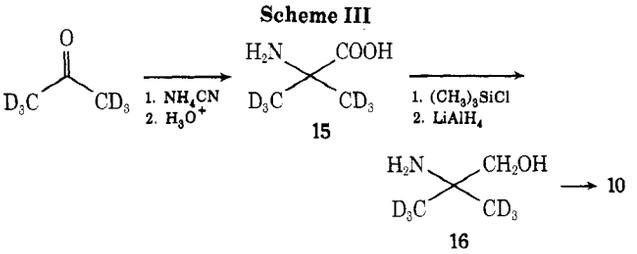


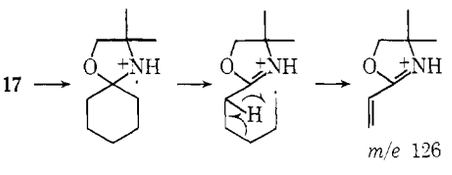
Figure 1. Mass spectrum of **17**.

Scheme III



For purposes of comparison the mass spectra of the precursor oxazolidines **17–23** were determined first. These spectra are characterized by the dominance of one or two peaks, suggesting formation of relatively stable ions, as with ethylene ketals.[21] Figure 1 shows the mass spectrum of **17**, with the typically dominant base peak at *m/e* 126 accounting for 25% of the total ion current. The mode of formation of this base peak is given in Scheme IV. Confirmation of this pathway was obtained from the mass spectra of the deuterated oxazolidines **18** and **19**, which displayed base peaks at *m/e* 127 and 132, respectively. Oxazolidine **20** showed a base peak at *m/e* 126 and one nearly as intense at *m/e* 140 corresponding to the two modes of cleavage of the

Scheme IV



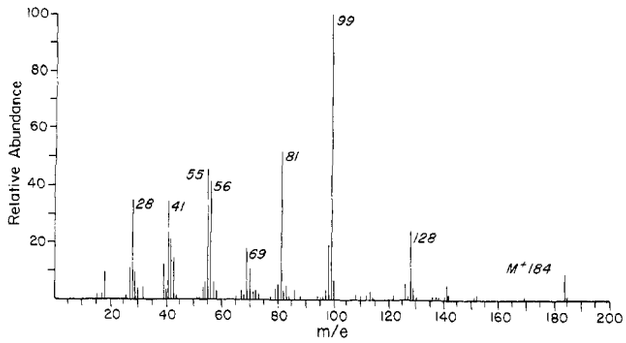


Figure 2. Mass spectrum of **1**. High-resolution data support the elemental compositions indicated, within an error of ±0.002 amu: C_3H_3O, C_4H_7, C_4H_8, C_5H_9, C_4H_7N, C_6H_9, C_5H_8NO, $C_6H_{10}O$, $C_6H_{12}N$, $C_6H_{11}O$, $C_6H_{11}NO$, $C_6H_{10}NO_2$, $C_7H_{11}NO_2$, $C_9H_{14}NO$.

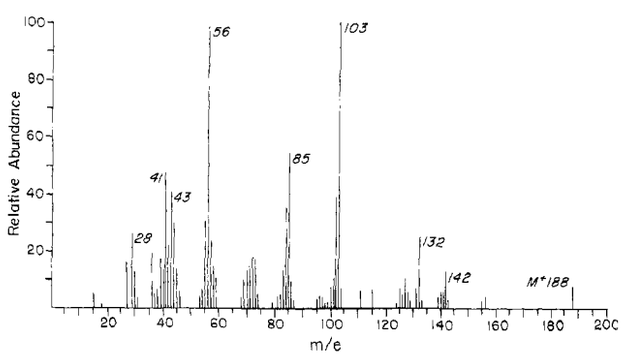


Figure 3. Mass spectrum of **9**.

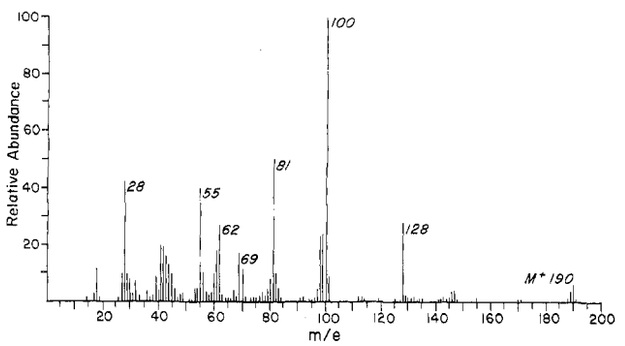


Figure 4. Mass spectrum of **10**.

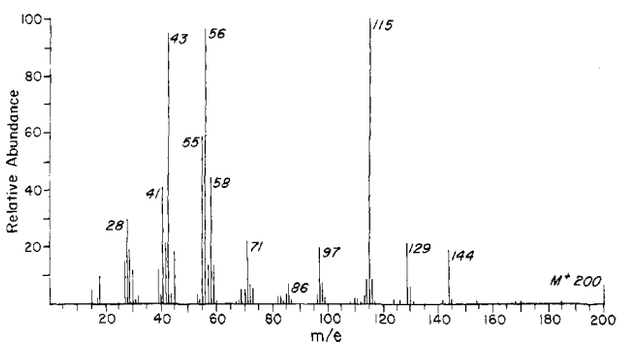


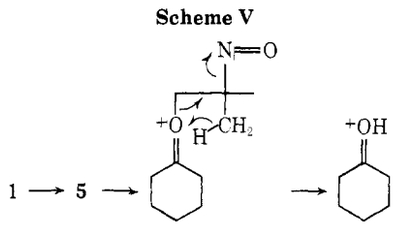
Figure 5. Mass spectrum of **13**. High-resolution data support the elemental compositions indicated, within an error of ±0.002 amu: C_4H_7, C_4H_8, C_3H_6N, C_2H_4NO, C_3H_6O, C_3H_8N, C_4H_9N, C_5H_{11}, C_4H_8NO, $C_5H_{12}N$, $C_6H_{11}N$, C_7H_{13}, $C_7H_{15}O$, $C_6H_{11}NO_2$, $C_7H_{14}NO_2$.

cycloalkyl ring. **22** showed peaks at *m/e* 114 and 170 reflecting loss of one or the other of the alkyl groups.

The mass spectra of the doxyls (see Figures 2–5) are markedly different. The dominant peaks reflect ions which tend not to retain charge on nitrogen, a pattern also found with other nitroxides.[15-18] The ether oxygen does, however, retain its charge-stabilizing capability, and has a profound influence in the spectrum. As will be demonstrated in the following, the fragmentation patterns of doxyls, *e.g.*, **1**, can be best represented as proceeding *via* a molecular ion of the same type, *e.g.*, **5**, encountered above in the chemical oxidation of these nitroxides.

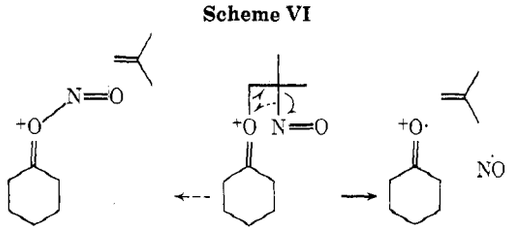
For all the doxyls the base peak occurs at M − 85, one mass unit higher than the molecular weight of the parent ketone. High-resolution data for **1** and **13** show that this peak corresponds in elemental formula to protonated ketone. The most plausible pathway for formation of protonated ketone is illustrated for doxyl **1** in Scheme V. The initially formed molecular ion **5** undergoes the familiar fragmentation to **6**, which forms protonated ketone **24** *via* intramolecular hydrogen atom abstraction as shown.[22] That the proton on oxygen in **24** originated in the heterocyclic *gem*-dimethyl group is proved by the shift of the base peak to one mass unit higher with **10** (Figure 4).

Scheme V

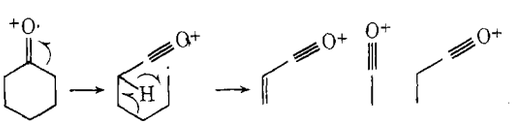


Peaks are present in the mass spectrum of **1** which indicate that oxonium ion intermediate **6** can also decompose with elimination of isobutene to form **25** (*m/e* 128), *via* an unusual intramolecular transfer of NO, or of isobutene and nitric oxide to form **26** (*m/e* 98) as shown in Scheme VI. Structures **25** and **26** are in accord with high-resolution data, and all the other doxyls have peaks of analogous origin. In particular, the peak at *m/e* 128 is shifted to *m/e* 132 in **9** and remains unchanged in **10**.

Scheme VI

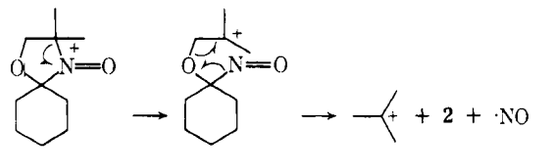


It should be noted that ion **26** is the molecular ion of cyclohexanone. Consequently, the more intense ions in the spectrum of the parent ketone **2** should also be significant in the spectrum of doxyl **1**. Such is the case. The base peak from cyclohexanone is due to **27** with *m/e* 55.[23] High-resolution measurements and shifts in the mass spectra of **9** and **10** (particularly the enhancement of the *m/e* 56 peak from **9**) allow at least a substantial portion of the *m/e* 55 ions to be assigned structure **27**. Similarly, the peaks at *m/e* 43 from **13** and *m/e* 57 from **14** can reasonably be assigned structures **28** and **29** as major contributors.



The mass spectral data suggest that some degree of fragmentation of molecular ion **5** occurs by the alternate path shown in Scheme VII, leading to tertiary carbonium ion **30** rather than oxonium ion **6.** This pathway is evidenced by the appearance in the spectra from all the nitroxides except **10** of a strong peak at *m/e* 56 arising from ion **31.** The appearance of a peak at *m/e* 62 with doxyl **10** (Figure 4) and high-resolution data for **1** and **13** support this interpretation.

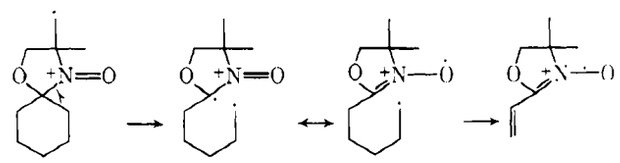
Scheme VII



5 30 31

A third pattern of fragmentation of molecular ion **5,** shown in Scheme VIII, is required to account for some relatively minor peaks which are especially noticeable in the mass spectra of the open-chain doxyls **13** (Figure 5) and **14.** The peaks at *m/e* 141 from **1** (**32**), *m/e* 129 from **13,** and *m/e* 143 from **14** have such an origin, as confirmed by high-resolution data for **1** and **13** and the shift to *m/e* 142 in the spectrum of **9.**

Scheme VIII



5 *m/e* 141

32

Finally, a number of lower mass ions can be readily explained as secondary fragmentation products. A prominent metastable at *m/e* 66.3 (calcd, 66.27) can be observed for the transition from **24** (*m/e* 99) to an ion with mass 81. High-resolution data confirm that this transition is a loss of H_2O leading to a $C_6H_9^+$ hydrocarbon fragment of uncertain structure.

The mass spectra of doxyl derivatives, although fairly complex, thus can be rationalized successfully on the basis of formation of an oxoammonium molecular ion like **5.** Although several fragmentation pathways are observed for the high-energy **5** produced upon electron impact, the principal pattern very reasonably is the same as that of **5** produced by chemical oxidizing agents.

Experimental Section

Low-resolution mass spectra were recorded with a Perkin-Elmer 270B double-focusing spectrometer using an ionizing voltage of 75 eV and a source temperature of 200°. Samples were introduced upon elution from a gas chromatograph equipped with a 20% SE-30 column operated with temperature programming at 20°/min from 70 to 200°, the eluted sample being passed through a Watson-Biemann molecular separator to remove most of the helium carrier gas. The spectrometer output was digitized by an auxiliary PDP-12 computer using a perfluorokerosene spectrum as reference. High-resolution mass spectra were recorded on an AEI MS-9 spectrometer using an ionizing voltage of 70 eV and a source temperature of 150°. Samples were introduced by direct insertion into the source; perfluorotributylamine was used as an internal standard. Nuclear magnetic resonance (nmr) spectra were recorded on a 60-MHz Perkin-Elmer R-24 spectrometer using CCl_4 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Shifts are reported in parts per million downfield from TMS. Infrared (ir) spectra were recorded on a Perkin-Elmer 137 spectrophotometer using potassium bromide pellets for solids (unless indicated otherwise) and thin films for liquids. Ultraviolet (uv) spectra were recorded on a Unicam SP800 spectrometer. Melting points were determined in open capillaries using Thomas-Hoover apparatus and are uncorrected. Elemental analyses are performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by Meade Microanalytical Laboratory, Amherst, Mass.

Gas chromatography (gc) was carried out either on a Perkin-Elmer 154 gas chromatograph using a 10 ft × 0.25 in. glass column packed with 30–60 mesh acid-washed Chromosorb P coated with 20% didecyl phthalate and operating at about 140° with a helium flow rate of 60 ml/min or on a Varian 2100 chromatograph using a 2 m × 4 mm glass column packed with 100–120 mesh Gas-Chrom Q coated with 3% of the indicated stationary phase and operating at about 100° with a nitrogen flow rate of 30 ml/min. The instruments used thermal conductivity and flame ionization detectors, respectively. In both cases peak areas are determined by Disc chart integration. In all yield determinations an appropriate internal reference compound was used, with prior determination of the relative detector response to reference and to the analyzed compound. Thin layer chromatography (tlc) was carried out on 5 × 20 cm plates coated with 0.25 mm thick layers of Merck silica gel $PF_{254+366}$ using various mixtures of ether and hexane as solvents. Preparative layer chromatography (preparative tlc) was generally carried out on 20 × 20 cm plates coated with 1.5 mm thick layers of the same silica gel using the solvents indicated. About 200 mg of material could be chromatographed per plate.

Commercial ketones used as starting materials were redistilled before use. The 2-amino-2-methyl-1-propanol and 85% *m*-chloroperbenzoic acid (Aldrich Chemical Co., Milwaukee, Wis.) were used as received. Deuterium oxide (99%) and acetone-d_6 (99.5%) were supplied by Stohler Isotope Chemicals, Rutherford, N. J. Reagent gases were supplied by Matheson Gas Products, E. Rutherford, N. J.

Preparation of Oxazolidines. Generally according to the procedure of Hancock and Cope,[24] the ketone (0.5 mol), 2-amino-2-methyl-1-propanol (0.8 mol), and *p*-toluenesulfonic acid (3.0 g) were refluxed under nitrogen in 150 ml of benzene for 8 hr with azeotropic water removal by means of a Dean-Stark apparatus. The product was diluted with 50 ml of ether, washed with 3 × 200 ml of water and once with saturated aqueous sodium chloride, and dried over Na_2SO_4. Evaporation of the solvent gave the crude oxazolidine derivative, which was fractionally distilled at reduced pressure to give the product as reported below.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane (**17**) was formed in 74% yield: bp 99–100° (24 mm) [lit.[24] bp 95–97.5° (20 mm)]; ir 3.04 and 9.62 μ; nmr ($CDCl_3$) δ 1.18 (s, 6), 1.51 (m, 10), and 3.43 (s, 2).

2,4,4-Trimethyl-2-pentyloxazolidine (**22**) was formed in 67% yield: bp 95° (15 mm) [lit.[24] bp 102–103° (19 mm)]; ir 3.00 and 9.55 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.6]undecane (**21**) was formed in 64% yield: bp 122–123° (23 mm); ir 2.97 and 9.58 μ; mass spectrum M^+ *m/e* 183; base *m/e* 126.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.11; H, 11.42; N, 7.63.

3,3,6-Trimethyl-1-oxa-4-azaspiro[4.5]decane (**20**) was formed in 80% yield: bp 108–109° (20 mm) ; ir 3.0 and 9.5 μ; mass spectrum M^+ *m/e* 183, base *m/e* 126.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.02; H, 11.54; N, 7.62.

2,2-Diethyl-4,4-dimethyloxazolidine (**23**) was formed in 22% yield (incomplete reaction): bp 89–91° (50 mm); ir 3.0 and 9.58 μ; nmr (CCl_4) δ 0.84 (t, 6), 1.17 (s, 6), 1.49 (q, 4), and 3.40 (s, 2); mass spectrum (high resolution) M^+ *m/e* 157.1460 (calcd for $C_9H_{19}NO$, 157.1466).

Preparation of Nitroxides. According to Keana's procedure,[1] a solution of 85% *m*-chloroperbenzoic acid (0.06 mol) in 80 ml of anhydrous ether was added dropwise over 15 min to an ice-cold, stirred solution of the appropriate oxazolidine derivative or secondary amine (0.05 mol) in 80 ml of anhydrous ether. The reaction mixture was allowed to warm to room temperature and stand for 12–24 hr. The product was washed with 4 × 75 ml of 5% aqueous sodium bicarbonate and once each with water and saturated aqueous sodium chloride and dried over $MgSO_4$, and the ether was evaporated to give the crude nitroxide.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy (**1**) was formed in 30% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane. A sample sublimed at 35° (0.1 mm) had mp 58–59° (lit.[1] mp 57–58°); ir 7.44 and 9.67 μ; uv max(Et_2O) 234 and 415 nm.

2,4,4-Trimethyl-2-pentyl-3-oxazolidinyloxy (13) was obtained as an orange oil which was not fully purified by distillation at 78–80° (0.3 mm) [lit.[1] 80° (0.08 mm)]. Chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane gave 11% yield of an orange liquid, ir 7.37 and 9.58 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.6]undec-4-yloxy (12) was obtained in 14% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane. A sample sublimed at 40° (0.05 mm) had mp 59–60°, ir 9.59 μ.

Anal. Calcd for $C_{11}H_{20}NO_2$: C, 66.62; H, 10.17; N, 7.06. Found: C, 66.59; H, 10.05; N, 6.63.

3,3,6-Trimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy (11) was obtained in 23% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane: bp 60° (0.1 mm); ir 7.32 and 9.67 μ.

Anal. Calcd for $C_{11}H_{20}NO_2$: C, 66.62; H, 10.17; N, 7.06. Found: C, 66.76; H, 10.10; N, 7.16.

2,2-Diethyl-4,4-dimethyl-3-oxazolidinyloxy (14) was prepared in 41% yield after chromatography on Florisil eluting with 5% ether in hexane: bp 60° (1.8 mm); ir 7.34 and 9.57 μ; mass spectrum (high resolution) M^+ *m/e* 172.1334 (calcd for $C_9H_{18}NO_2$, 172.1337).

2,2,6,6-Tetramethylpiperidinooxy (3) was obtained in 32% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with hexane. The crude 3 thus obtained purified itself by spontaneous sublimation within its container at room temperature and atmospheric pressure: mp 38–39° [lit.[12] mp 38–39°]; ir 7.37 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy-*6,6,10,10-d*$_4$ (9). Cyclohexanone-*2,2,6,6-d*$_4$ was prepared by treatment of cyclohexanone with D_2O containing potassium carbonate. This product was converted to oxazolidine 18 in the usual manner using 2-amino-2-methyl-1-propanol which had previously been treated with D_2O and had then been dried by azeotropic distillation with benzene. This labeled 18 (1.8 g) was treated with 85% *m*-chloroperbenzoic acid (2.0 g), as described earlier. Chromatography of the product on 40 g of Woelm acid-washed alumina (activity I) using 5% ether in hexane as eluent gave after sublimation at 38° (0.05 mm) 0.800 g of 9: mp 58–59°;[25] ir 4.54 and 9.73 μ; mass spectrum M^+ *m/e* 188, 75% d_4 species as estimated by molecular ion intensities.

2-Amino-2-methylpropanoic Acid-*d*$_6$ (15). Exactly according to the procedure of Steiger,[19] a solution of 9.0 g of acetone-d_6 in 25 ml of methanol was treated with an aqueous solution of 6.9 g of NaCN, 8.3 g of NH_4Cl, and 9.6 ml of NH_4OH to afford, after crystallization from absolute ethanol, 9.7 g (55%) of 15: mp >300°; no chloride ion by aqueous $AgNO_3$; ir 4.55, 6.15, and 8.76 μ.

2-Amino-2-methyl-1-propanol-*d*$_6$ (16). Following a published procedure,[20] 2.4 g of the oven-dried amino acid 15 prepared above was suspended in 100 ml of dry benzene which was then refluxed under nitrogen with 20 ml of freshly distilled triethylamine and 6 g of distilled chlorotrimethylsilane for 12 hr. The cooled mixture was filtered and dried (Na_2SO_4), and the benzene was evaporated. The residue containing the silyl derivative was dissolved in 200 ml of anhydrous ether and the resulting solution was added dropwise during 1 hr to a stirred, ice-cold solution of 0.95 g of lithium aluminum hydride in 150 ml of ether. After 1 hr at room temperature and 2 hr at reflux, the mixture was cooled in ice and 100 ml of water-saturated ether was added dropwise over 45 min with stirring. After filtration of the inorganic precipitate the solution was dried (K_2CO_3) and the ether was evaporated. The residue was heated with 1 ml of water on a steam bath for 1 hr; the mixture was saturated with potassium carbonate and extracted with ether. Evaporation of the extract gave 1.48 g of light yellow liquid containing 16 (ir 4.56 μ) which was used without purification in the next step.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane-*d*$_6$ (19). All of this product containing 16 was refluxed under nitrogen with cyclohexanone (1.8 g) and *p*-toluenesulfonic acid (1.0 g) in 150 ml of benzene for 10 hr with azeotropic water removal by means of a Dean-Stark apparatus. The work-up described earlier for oxazolidine preparation gave after distillation at 50° (1.5 mm) 0.58 g of 19, slightly contaminated with cyclohexanone: ir 4.54 and 9.63 μ; nmr 1.47 (br s, 10) and 3.42 (s, 2); mass spectrum M^+ *m/e* 175, deuterium incorporation about 90% by nmr.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy-*d*$_6$ (10). A solution of 85% *m*-chloroperbenzoic acid (0.8 g) in 30 ml of anhydrous ether was added dropwise over 15 min to a stirred, ice-cold solution of oxazolidine derivative 19 (0.55 g) in 30 ml of anhydrous ether. After 4 hr at room temperature the mixture was worked up as described earlier. Chromatography on 10 g of Woelm acid-washed alumina (activity I) gave upon elution with hexane and 5% ether in hexane 0.081 g of orange solid 10: mp 58–59°; ir 4.48 and 9.87 μ; mass spectrum M^+ *m/e* 190, 55% d_6 species and 35% d_5 species as estimated by molecular ion intensities.

Reactions of Nitroxides with Oxidizing Agents. All reactions were carried out at room temperature. Solutions were flushed with nitrogen for 30 min prior to introduction of the reactant gas. Only glass equipment was used in these reactions.

Reactions of Doxyls with Commercial Nitric Oxide. In a general procedure, 1 mmol of the appropriate nitroxide was dissolved in 10 ml of solvent together with a known, approximately equal weight of an unreactive internal reference compound whose gc retention time did not coincide with that of starting material or any of the products. Upon bubbling commercial nitric oxide (from a tank) through the solution for 5 min, the initially light orange color of the solution deepened and then turned green or blue, finally lightening to a yellowish, sometimes cloudy mixture. Samples of this mixture were analyzed by gc. The predominant product was shown to be the parent ketone by correspondence of gc retention times, and also in the case of 1 by a mass spectrum from the eluted gc peak. The yield of ketone was determined by the relative areas of the product and reference peaks; averages from two or more chromatograms are reported in Table I.

Reaction of 3 with Commercial Nitric Oxide. Treatment of 100 mg (0.642 mmol) of 3 in 5 ml of cyclohexane with commercial nitric oxide for 4 min gave a bright yellow precipitate which was filtered and washed with hexane to give 130 mg (93%) of **4d:** mp 110–120° dec; ir (Nujol mull) 6.2 μ; uv max (CH_3CN) 244 nm (ε 1680) and 450 (26); positive brown ring test with H_2SO_4–$FeSO_4$ for nitrate ion.

Anal. Calcd for $C_9H_{18}N_2O_4$: C, 49.53; H, 8.31; N, 12.84. Found: C, 49.75; H, 8.25; N, 12.97.

Reactions with Purified Nitric Oxide. Solutions of nitroxides 3 and 11 were treated in the same manner with nitric oxide which had been passed through 3 *N* aqueous sodium hydroxide and sodium hydroxide pellets to remove the nitrogen dioxide. No reaction occurred (as monitored by gc) even after 0.5–1 hr of treatment. Injection of air at this point rapidly initiated the reaction observed with unpurified commercial nitric oxide.

Reaction of 1 with Nitrogen Dioxide. Commercial nitrogen dioxide was bubbled through a solution of 187 mg (1.02 mmol) of 1 and 73.6 mg of dodecane in 5 ml of cyclohexane for 30 sec. Cyclohexanone was formed in 65% yield as determined by gc.

Reaction of 1 with Chlorine. Dry chlorine was bubbled through a solution of 300 mg (1.63 mmol) of 1 in 5 ml of ether until the initially orange solution was deep green (about 2 min). Cyclohexanone and 2-chlorocyclohexanone were identified as products by comparison of gc retention times with those of commercially available samples of the authentic ketones on two columns (SE-30 and QF-1). Evaporation of the solvent followed by preparative tlc (20% ether in hexane) gave 2-chlorocylohexanone (10 mg) and 7 as a blue oil (50 mg): ir 8.0 and 8.92 μ; nmr ($CDCl_3$) 1.19 (s), 1.6–2.5 (m), 3.8–4.9 ppm (m). The latter formed a white powder upon standing at −10°. Trituration with petroleum ether gave 9.5 mg: mp 101–103° (melt was a dark blue liquid); ir 7.93 and 8.85 μ; uv max (95% EtOH) 295 nm; nmr (CCl_4) δ 1.17 (s), 1.5–2.0 (m), 4.0–4.7 (m).

Oxidation of 7 with *m*-Chloroperbenzoic Acid. Crude blue oily 7 (120 mg) was dissolved in 20 ml of chloroform and added dropwise over 5 min to a refluxing solution of 85% *m*-chloroperbenzoic acid (2.0 g) in 20 ml of chloroform. Refluxing was continued for another 5 min, during which the reaction mixture became colorless. The cooled mixture was diluted to 60 ml with chloroform and washed twice with 50-ml portions of 10% aqueous sodium sulfite and twice with saturated aqueous sodium bicarbonate. The chloroform layer was separated, dried over $MgSO_4$, filtered, and evaporated. Chromatography of the residue on Woelm base-washed alumina (activity III) gave upon elution with hexane 26.4 mg of 8. Preparative tlc of this material on Merck silica gel $PF_{254+366}$ impregnated with KOH with 40% ether in hexane as solvent gave in one band 20 mg of a clear liquid: ir 6.53 μ; nmr (CCl_4) 1.63 (s, 6), 1.6–2.3 (m, 6), 4.07 (s, 2), 4.1–4.7 (m, 2); mass spectrum weak M^+ *m/e* 303, 305, and 307.[26]

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Concentration Effects in the Photochemical Syn–Anti Isomerization of an Oxime Ether

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Upon irradiation with ultraviolet light, the *O*-methyl oxime ethers of 2-acetonaphthone undergo facile syn–anti photoisomerization. At low concentrations the syn isomer predominates in the photostationary state. High oxime ether concentrations, however, were found to enhance the fraction of the anti isomer in the photoequilibrium. Evidence supporting the involvement of the singlet state was obtained from fluorescence quenching studies and photosensitized isomerization experiments. Fluorescence quenching of both isomers by 1,3-cyclohexadiene was found to be more sensitive toward the quencher concentration than chemical quenching. The excited syn isomer was much less sensitive toward chemical quenching and showed a less intense emission than the corresponding anti form. The data obtained are consistent with the involvement of an excimer which is capable of inducing efficient syn–anti isomerization and whose decay ratio differs from that of excited monomer.

The thermal[3-9] and photo-[10-33] interconversions of the syn and anti isomers of imines are a subject of long-standing interest. The mechanism for the thermal interconversion of imine diastereomers is currently the subject of considerable debate,[34-45] and has been considered in terms of either a planar inversion mechanism or a rotation mechanism. The rotation or torsion mechanism involves a twisting about the C=N double bond. The inversion mechanism, on the other hand, is characterized by an increase in the angle of the C=N–C bond from approximately 120° in the ground state to 180° in the transition state. Evidence obtained from studies of substituent effects (steric and electronic) suggests that most simple imines interconvert by the inversion mechanism,[44] although some of the results obtained have been considered to be inconclusive.[34-36]

The mechanism by which the syn and anti isomers of imines are interconverted in the excited state is even more complicated. Whether isomerization about the C=N double bond proceeds by rotation or linear inversion remains to be clarified. A major complication with the photochemical studies is that the thermal barrier between the two diastereomers of most imines is sufficiently low that the photochemically induced shift in the configurational equilibrium is only temporary at ambient temperatures and is frequently followed by a rapid, thermal relaxation which reestablishes the initial configurational equilibrium between the syn and anti isomers.

In previous work[31] we showed that irradiation of an oxime ether brings about a rapid syn–anti isomerization. The oxime ether molecule is an attractive system for mechanistic photostudies, since the presence of the methoxyl group drastically reduces the rate of thermal interconversion of the syn and anti forms (*i.e.*, $k < 10^{-13}$ at 60°)[3] and allows mechanistic studies to be carried out at ambient temperatures.

In order to secure additional information on the reactivity of the excited state(s) involved in the syn–anti photoisomerization reaction, we decided to study the photochemistry of a naphthyl-substituted oxime ether. It is reasonable to assume that in the naphthyl oxime ether system, the excitation energy will be heavily localized on the