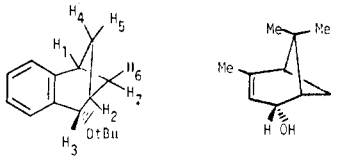


13 14

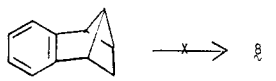
(9) Abraham, R. J.; Cooper, M. A.; Salmon, J. R.; Whittaker, D. *Org. Magn. Reson.* **1972**, *4*, 489–507.

(10) A trace (1.3%) of such a product is formed by the 2-norbornenyl cation generated by irradiation of an alkaline alcoholic solution of 5-norbornen-2-one tosylhydrazone. Cf. Kirmse, W.; Siegfried, R. *Chem. Ber.* **1972**, *105*, 2754–2763.[11] For related studies on the norbornyl system, see also: Siegfried, R. *Ibid.* **1974**, *107*, 1472–1482. Blattel, R. A.; Yates, P. *Tetrahedron Lett.* **1972**, 1073–1076. Note that bridge migration in **1** and **3** is occurring from an exo precursor.[7]

(11) The method is that of Dauben, W. G.; Willey, F. G. *J. Am. Chem. Soc.* **1962**, *84*, 1497–1498.

(12) For other examples of the formation of hot carbenium ions by photolysis of halides, see Takaishi, N.; Miyamoto, N.; Inamoto, Y. *Chem. Lett.* **1978**, 1251–1252, and references therein.

(13) The di-π-methane product of benzonorbornadiene (**15**) is observed in the methanol photolysis of **1** at higher conversions and could conceivably be a precursor to **8**. In fact, it is clearly a secondary photoproduct, while **8** is detectable immediately upon the onset of photolysis. Furthermore, **15** does not solvolyze to **8** under ground-state or excited-state conditions.



15

(14) The B_{2u} band for **3** is virtually identical with that of **4**.

(15) Jaeger, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 6401–6402. We find 2-phenylethyl chloride to be unreactive under our conditions.

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(18) Kropp, P. J.; Gibson, J. R.; Snyder, J. J.; Poindexter, G. S. *Tetrahedron Lett.* **1978**, 207–210, and references therein.

(19) The *ionic* products from benzyl chloride appear to be primarily *triplet* derived and the *radical* products *singlet* derived.[17]

(20) For an excellent discussion, see Cristol, S. J.; Stull, D. P.; Daussin, R. D. *J. Am. Chem. Soc.* **1978**, *100*, 6674–6678.

(21) That the high exo/endo reactivity ratio is *not* due to a high rate of endo recombination is evidenced by the considerably shortened singlet lifetime of **1** (<1 ns) relative to **2** (10.9 ns) in methanol.

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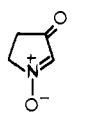
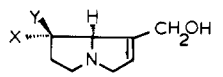
Functionalized Nitrones. A Highly Stereoselective and Regioselective Synthesis of *dl*-Retronecine

Sir:

The use of nitrones in organic synthesis has developed quite rapidly in recent years;[1] however, while the use of functionally modified cyclic nitrones (e.g. **1**) appears to offer an increased



1



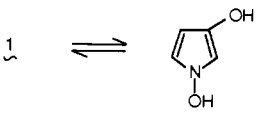
2a, X = Y = H
b, X = H, Y = OH
c, X = OH, Y = H

synthetic potential, the fact that such nitrones have not been so utilized reflects the problems associated with their preparation.[2] One objective of this report is to note that certain nitrones of this type can be produced in good yield by rational chemical pathways and, moreover, that they are relatively stable and undergo the 1,3-dipolar cycloaddition reactions characteristic of their nonfunctionalized counterparts. We have been particularly concerned with the efficient generation of cyclic α-keto nitrones or their functional equivalents.

A motivating influence on our interest in cyclic α-keto nitrones stems from a desire to design a synthesis of *dl*-retronecine,[3] the most widely occurring[4] of the necine bases,[5] which, because of its center of unsaturation, exhibits marked hepatotoxic and antitumor properties.[6,7]

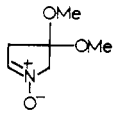
Indeed, the macrocyclic lactones (e.g., senecionine) derived from this base display the most profound antitumor activity in the entire Senecio class of alkaloids.[7] It should be noted that the most important physiological activity rests with those pyrrolizidine alkaloids derived from necine bases having a double bond between C-1 and C-2 (e.g., supinidine (**2a**), retronecine (**2b**), and heliotridene (**2c**)).

Although we have previously demonstrated[1a] that *dl*-supinidine (**2a**) can be assembled from a simple, unfunctionalized nitrone precursor, the synthesis of *dl*-retronecine (**2b**) demands the involvement of a functionalized nitrone in order to make provision for the hydroxyl group at C-7. Clearly, 3-keto-1-pyrroline 1-oxide (**1**) could provide a point of departure for our synthesis of **2b.** Unfortunately, we were aware from the outset of the possible isomerization of **1** to its hydroxypyrrole tautomer **3.** Thus, we chose to circumnavigate this potential



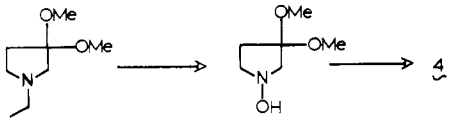
3

difficulty by focusing our initial efforts on a functional equivalent of **1,** namely the nitrone ketal **4.** We considered that efforts to generate **4** from the corresponding hydroxylamine **6** must confront the problem of regiochemistry (i.e., the possible production of mixtures of **4** and **5**); however, we expected



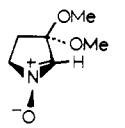
5

that the desired nitrone would predominate.[8] Thus, we transformed *N*-ethylpyrrolidin-3-one[9] into the corresponding dimethyl ketal (methyl orthoformate, HCl, MeOH), and thence into the hydroxylamine **6** according to the usual N-oxidation,



6

Cope elimination sequence.[1a] To our pleasant surprise, the mercuric oxide mediated oxidation of **6** proceeded regiospecifically to give nitrone **4** (97%), which exhibits typical absorptions at 6.25 and 7.2 μ (IR). The NMR spectrum ($CDCl_3$, 100 MHz) displays signals at δ 7.12 (t, 1 H, $J \simeq 1.5$ Hz), 4.06 (dt, 2 H, J = 7 Hz, 1.5 Hz), 3.28 (s, 6), and 2.4 ppm (t, 2 H, J = 7 Hz) entirely consistent with the structural assignment. This remarkable selectivity may be related to a diminution of



4a

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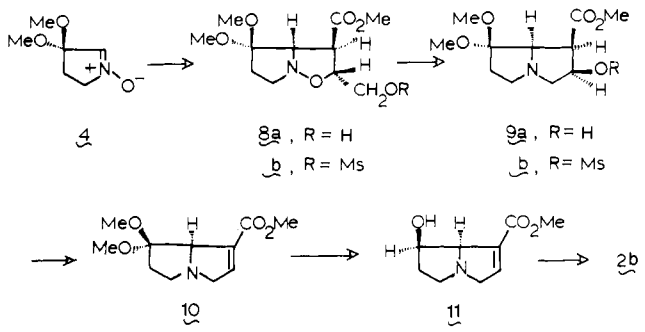
Scheme I



eclipsing interactions (i.e., to a more favorable dihedral angle relationship) in proceeding from **6** to **4** (cf. **4a**).[10]

Although it was envisaged that steric factors might retard the addition of **4** to methyl γ-hydroxycrotonate, in fact this reaction proceeds smoothly in chloroform at 45 °C to provide isoxazolidine **8a** in 86% yield[11] (Scheme I).

The regiochemical assignment is consistent with those previously observed for various crotonate-nitrone cycloadditions[1a,12] and is reinforced by the spectral similarity of **8a** to the isoxazolidine[1a] derived from 1-pyrroline 1-oxide and the same dipolarophile. Isoxazolidine **8a** exhibits the expected three singlets (NMR) at δ 3.20, 3.68, and 3.76 ppm, attributed to the three methyl groups. Conversion of **8a** into the corresponding mesylate **8b** ($MeSO_2Cl$, Et_3N, CH_2Cl_2) in 99% yield is accompanied by the loss of hydroxyl stretching absorption (~3 μ) with persistence of carbonyl absorption (5.77 μ) in the IR spectrum. Moreover, an additional methyl resonance appears at δ 3.10 ppm (NMR). While the NMR spectra of **8a** and **8b** suggest the presence of a diastereomeric mixture of adducts, this factor in no way complicates our synthetic objectives since the chirality at both C-2 and C-3 is subsequently annihilated.

The hydrogenolysis of the nitrogen-oxygen bond at **8b** (Pd/C, H_2, MeOH) leads to the formation **9a** (84%) by the concomitant displacement of the mesylate by the newly liberated secondary amine function. The pyrrolizidine **9a**, IR ($CHCl_3$) 2.84 (OH) and 5.78 μ (C=O), incorporates three three-proton singlets at δ 3.19, 3.22, and 3.71 ppm in the NMR spectrum. The mass spectrum exhibits a molecular ion at *m/e* 245.

Conversion of the β-hydroxy ester **9a** into the corresponding mesylate **9b** was followed by triethylamine-mediated elimination to give the α,β-unsaturated ester **10** (98%). The carbonyl absorption of **10** appears at 5.80 μ (IR), while its NMR spectrum contains the vinyl signal at δ 6.64 ppm (br s, 1) and three methoxyl signals at δ 3.75 (s, 3, CO_2Me), 3.20 (s, 3, OMe), and 3.36 ppm (s, 3, OMe). The ketone (81% yield) derived from **10** by hydrolysis (37% hydrochloric acid, DME) shows pronounced thermal lability even at 0 °C and was therefore rapidly reduced to the corresponding alcohol ester **11**, mp 122–123 °C, with sodium borohydride in methanol. This alcohol exhibits spectral properties identical with those recorded by Culvenor,[13] who obtained **11** from natural *d*-retronecine.

The hydroxy ester **11** was converted into *dl*-retronecine by reduction with alane in THF.[14] The *dl*-retronecine (mp 130 °C, lit.[9] mp 130–131 °C) so obtained possessed IR and NMR spectral properties identical with those of an authentic sample of *dl*-retronecine.

In an effort to provide the efficient synthesis delineated above with even further economy, we attempted to generate the α-keto nitrone **1** from the ketal **4.** Indeed, exposure of **4** to 1% hydrochloric acid at 0 °C for 1 h resulted in the generation of the nitrone as indicated by an absence of the methoxyl singlets, and the presence of the nitrone proton at C-2, δ 7.15 ppm (s, 1), in the NMR spectrum; however, the solution containing this α-keto nitrone darkened rapidly. Clearly, the ketal nitrone **4** offers the greater synthetic potential.

Acknowledgment. We thank the Institute of General Medical Sciences (NIH) for financial assistance (GM 25303). Moreover, we thank Dr. A. R. Mattocks (Medical Research Council Laboratories; Surrey, England), Dr. C. C. J. Culvenor (CSIRO), Dr. D. J. Robins (Glasgow), and Dr. M. Suffness (Developmental Therapeutics Program, NCI) for samples of *d*-retronecine.

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(1) For example, see: (a) Tufariello, J. J.; Tette, J. P. *J. Chem. Soc., Chem. Commun.* **1971,** 469–470. (b) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976,** 4037–4040. (c) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976,** *98,* 6722–6723. (d) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovič, M. *Ibid.* **1978,** *100,* 6291–6292. (e) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, Sk. Asrof *Ibid.* **1979,** *101,* 2435–2442.
(2) For example, 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide has been prepared from 2-methyl-1-pyrroline 1-oxide in <6% yield using selenium dioxide: Brown, R. F. C.; Subrahmanyan, L.; Whittle, C. P. *Aust. J. Chem.* **1967,** *20,* 339–347. A synthesis of 5,5-dimethylpyrroline 1-oxide, which is incapable of tautomerization into a pyrrole, could not be adapted to the synthesis of **1:** Clark, V. M.; Sklarz, B.; Todd, A. *J. Chem. Soc.* **1959,** 2123–2127.
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(4) For a review, see Warren, F. L. *Fortschr. Chem. Org. Naturst.* **66,** *24,* 329–406.
(5) For recent synthetic efforts directed toward the saturated pyrrolizidine alkaloids, see: Robins, D. J. *Alkaloids (London)* **1978,** *8,* 47–61. Danishevsky, S. *Acc. Chem. Res.* **1979,** *12,* 66–72. Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978,** *43,* 4662–4663.
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(10) For a related transformation similarly rationalized, see Bonnett, R.; Ho. S. C.; Raleigh, J. A. *Can. J. Chem.* **1965,** *43,* 2717–2723.
(11) Although two diastereomeric adducts are formed, the depiction of **8a** in Scheme I is that of the major stereoisomer. The reasons for this stereochemical assignment will be detailed in a full report.
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Structural Dependence of ^{18}O Isotope Shifts in ^{13}C NMR Spectra

Sir:

Isotopic substitution with ^{18}O causes shifts in the NMR resonance positions of attached nuclei such as ^{55}Mn, ^{95}Mo, and ^{31}P which are useful in mechanistic studies.[1] Recently Risley and Van Etten confirmed[2] theoretical prediction[3] of an ^{18}O isotopic effect on ^{13}C NMR spectra by observing an upfield shift for [^{18}O]-*tert*-butyl alcohol. We now report that the ^{18}O-induced upfield shift in natural-abundance ^{13}C NMR spectra appears to be a general phenomenon, and that its magnitude is dependent on structure.

The ^{18}O-labeled compounds listed in Table I were prepared,[4] and their natural-abundance ^{13}C NMR spectra were measured on a Bruker WH 400 instrument at 100.6 MHz in the Fourier

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