venient low-temperature source for 1,6-dioxyl radicals. The thermal and photochemical products were carbon dioxide, ethylene, and acetone (60–65%) and 3,3,6,6-tetramethyl-1,2-dioxane (18%).

The cyclic dialkyl peroxides which have received considerable attention are the 1,2-dioxetanes **15**,[36] the 1,2-dioxolanes **16**,[37] and the 1,2-dioxanes **17**.[35] With the help of the mechanistic tools that were described in the elucidation of the β-peroxylactones, the respective diradicals were postulated as reaction intermediates.

Among the cyclic diacyl peroxides, the malonyl peroxides **18**[38] and the succinyl peroxides **19**[39] have been worked on. The thermal and photochemical decarboxylation of the malonyl peroxides **18** gave cleanly the elusive α-lactones. Consequently, these substrates seem to be of little use for the generation of oxygen diradicals.

The succinyl peroxide **19**, on the other hand, was a fruitful system for mechanistic elucidation of dioxyl radicals. Using the *meso*- and *dl*-dimethylsuccinyl derivatives, it was shown[39] that the same ratio of *cis*- and *trans*-2-butenes, 61% and 28%, respectively, and the same ratio of *meso*- and *dl*-β-lactones, 10% and 3%, respectively, were formed from both diacyl peroxides **22a,b**. A 1,4-diradical was proposed to account for these interesting experimental data.

Finally, work on the thermal decomposition of bicyclic dialkyl peroxides is beginning to appear.[40] However, rigorous mechanistic studies seem to be in order for the full exploration of the conformationally anchored dioxyl intermediates. Such mechanistic investigations are timely, urgent, and important. We foresee a great deal of mechanistic activity on the versatile and fascinating dioxyl intermediates and certainly encourage it.

I wish to express my gratitude to my students, whose names are referenced in the bibliography, for their enthusiastic and dedicated collaboration. Without their diligent efforts there would be no Account. Our work was supported by the National Institutes of Health, National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, the Guggenheim Foundation, the Sloan Foundation, Research Corporation, Western Fher Company, Eli Lilly Company, and the University of Puerto Rico.

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Alkaloids from Nitrones

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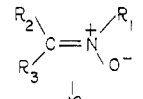
Although the education of the organic chemist has traditionally involved an exposure to the chemistry of a plethora of functional groups, only recently has significant attention been focused on the important chemistry of certain 1,3-dipolar functionalities.[1-3] Indeed, applications of these dipolar substrates to the synthesis of natural products has been a very recent development.[4,5] Noteworthy is the elegant application of nitrile oxide chemistry to the synthesis of corrins.[4] We have been long convinced that nitrones, in particular, offer unique advantages in total synthesis. The nitrone functionality (cf. 1), so designated because of an ob-



served chemical relationship to ketones,[6] is a 4-π-electron system capable of undergoing reaction with other multiply bonded systems in a process not unlike the Diels–Alder reaction. Although the addition of nitrones to phenyl isocyanate was described in the last century,[7] their additions to alkenes were reported relatively recently and independently by three separate groups.[8-10] The brilliant efforts of Huisgen[1,11] are largely responsible for the important and systematic exploration of intermolecular 1,3-dipolar cycloadditions to afford five-membered heterocycles ([3 + 2] cycloadditions),[3,11] while LeBel[12] is responsible for the pioneering investigations of the factors influencing intramolecular nitrone–alkene cycloadditions.

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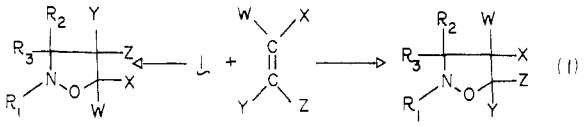
The reactions of nitrones with alkenes (cf. eq 1) proceed to the isoxazolidine[13] stage. In principle, two



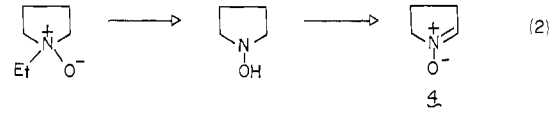
(1)

regioisomeric adducts can emerge from such cycloadditions. These reactions, originally depicted as concerted processes,[1,11] have also been treated as stepwise reactions involving diradical intermediates.[14] Although the mechanistic aspects of these transformations have generated discussion,[11,14] their synthetic applications have fluorished.[15]

Nitrone Synthesis

We have determined that even quite reactive nitrones can be conveniently prepared and handled in solution to avoid the problems of di- or trimerization common to certain of them. Some nitrones (e.g., *C,N*-diphenylnitrone) are quite stable and are commercially available. Alternatively, nitrones are readily obtained by the direct condensation of N-substituted hydroxylamines with aldehydes or ketones (e.g., *C*-phenyl-*N*-methylnitrone from methylhydroxylamine and benzaldehyde).[15]

N,N-Disubstituted hydroxylamines can be readily oxidized to nitrones by a variety of oxidants, perhaps most commonly with yellow mercuric oxide. The procedure which follows is illustrative of the general method we have utilized. After being stirred for 4 h at −10 °C in methylene chloride containing the hydroxylamine and 2 equiv of mercuric oxide, the reaction mixture is filtered to remove mercury salts and the nitrone (85–90%) is used without isolation. The hydroxylamines themselves are frequently obtained by Cope elimination from the corresponding tertiary amine oxides (cf. eq 2). Nitrones can also be generated from a

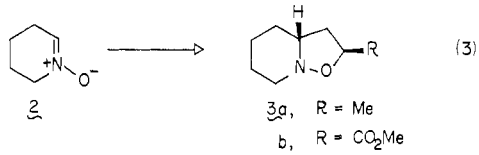


(2)

4

variety of other functional substrates.[15b]

Advantages. Even at the outset of our investigations, we realized that nitrones could offer five potential advantages in the synthesis of alkaloids. First, a nitrogen is incorporated within the functional moiety itself which can provide for an amino grouping of the natural system. Second, a crucial carbon–carbon bond is formed. Reactions involving the formation of such bonds are naturally highly desirable. Third, an oxygen is transferred to a carbon of the dipolarophile. This "oxidation" process is of enormous utility in providing for the introduction of relevant functionality in the natural system. Fourth, when we began our investigations it was clear that the regiochemical integrity of these reactions held the key to the efficacy of the method. It was deemed essential that cycloadditions of the type depicted in eq 3 proceed in only one of the two



(3)

2

3a, R = Me
b, R = CO_2Me

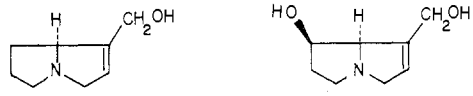
possible regiochemical senses (e.g., to give **3a** from **2** and propylene) and, moreover, that this mode be predictable. The degree to which these requirements are met is discussed below. Finally, in certain cases, a knowledge of the stereochemistry of the cycloadditions (e.g., to give **3** rather than its diastereomer) was deemed important with regard to our synthetic objectives.

Clearly, the first three of these potential advantages are of unquestioned utility in the synthesis of alkaloids. Prior to the initiation of our studies we were aware that the last two of the potential advantages could in actuality become serious obstacles.

Senecio Alkaloids

***dl*-Supinidine.** The synthesis of alkaloids has long provided a particularly severe challenge to the organic chemist owing to the structural diversity and complexity associated with this family of compounds. Only recently has attention been directed at general approaches[16–18] capable of multiply penetrating this group of natural products and elaborating a wide variety of alkaloidal skeleta.

We considered it prudent in our attempts to apply nitrone methodology to alkaloid synthesis to concentrate our initial efforts on targets of modest structural complexity. With this consideration in mind, we chose as our initial target molecule the necine base *dl*-supinidine (**5**), derived from the genus *Senecio*. Supinidine



5 supinidine 6 retronecine

and retronecine (**6**) occur naturally both as the free base and in esterified form.[19] The unsaturated Senecio alkaloids display both hepatotoxic and antitumor properties.[19d–f] Supinidine itself had proven to be a surpisingly elusive target for the synthetic chemist.[20]

In this initial nitrone-based synthetic endeavor, we were compelled to confront the question of the regiochemical preferences of nitrone cycloadditions to unsymmetrical dipolarophiles.[21] It was known from the

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(20) (a) N. K. Kochetkov, M. Likhosherstov, and A. S. Lebedeva, *Zh. Obshch. Khim.*, **31**, 3461 (1961); (b) M. D. Nair and R. Adams, *J. Org. Chem.*, **26**, 3059 (1961); (c) B. M. Goldschmidt, *ibid.*, **27**, 4057 (1962); Approaches to *dl*-Supinidine, University Microfilms, Inc. No. 62-2241.
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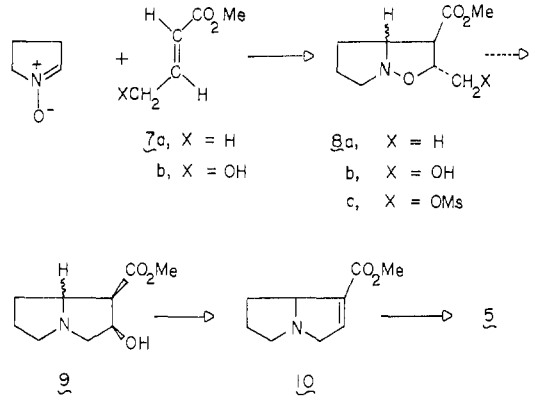
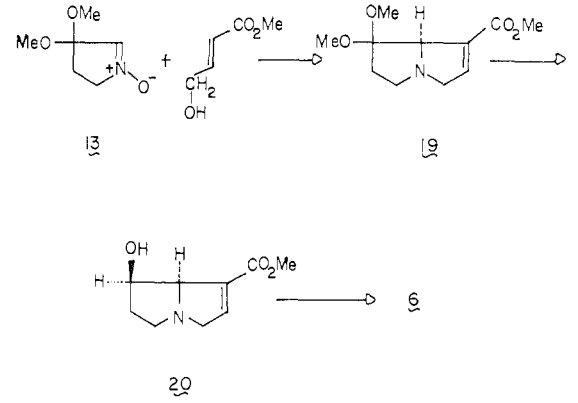
Scheme I

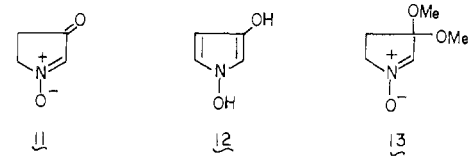


Scheme II

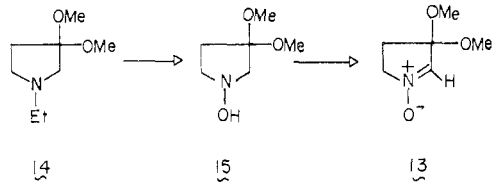


outset of our work that monosubstituted alkenes would undergo cycloaddition with nitrones to afford 5-substituted isoxazolidines.[1,15b] Thus 3,4,5,6-tetrahydropyridine 1-oxide (**2**) reacts with both methyl acrylate and propylene to provide adducts **3a** and **3b**, respectively (cf. eq 3). This tendency toward regioselectivity is most readily explicable through the use of frontier orbital considerations.[22-26] Investigations[21,27,28] of the additions of crotonates (e.g., **7a** and **7b**) to nitrones suggest that, in contrast with the results obtained for acrylates, β-oxa esters (e.g., **8a**) are produced irrespective of the geometry of the double bond in the dipolarophile (i.e., 1-butenolide affords the same regiochemical outcome).[17] These findings also appear to be consonant with a frontier orbital approach.[11,29] The unexpectedly high regioselectivity observed for these cycloadditions in the desired sense prompted the completion of the synthesis (Scheme I) of *dl*-supinidine by hydrogenolytic scission of the nitrogen–oxygen bond of the corresponding mesylate **8c**, accompanied by the cyclization of the resulting amino alcohol to give pyrrolizidine **9**. The overall process involves a transfer of oxygen from the nitrogen of the nitrone to the carbon of the dipolarophile at the center required for the facile dehydration of **9** to the unsaturated ester **10**, and thence to *dl*-supinidine by alane reduction.[21] Thus, although the nitrone oxygen has been eliminated during the course of the synthetic excursion, it has played a central role in the outcome.

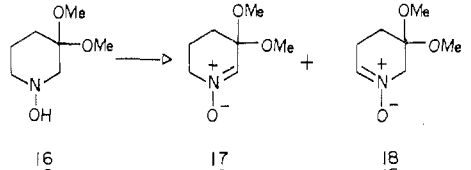
***dl*-Retronecine.** The necine base retronecine (**6**), a close relative of supinidine, is a constituent of a number of physiologically important pyrrolizidine alkaloids (cf. senecionine).[19] The synthetic approach envisioned for this Senecio alkaloid relies on the synthesis of a functionally modified nitrone (Scheme II). The keto nitrone **11** could in principle serve as a point of departure for this synthesis save for its potential isomerization to the corresponding hydroxypyrrole **12**. For this reason,



we chose[30] the nitrone ketal **13** as an initial target. Amine ketal **14**[31] was converted into the hydroxylamine **15** via a Cope elimination from the corresponding amine



oxide. Our earlier work[32] with the functionalized six-membered hydroxylamine ketal **16** indicated that mercuric oxide induced oxidation of **16** led to an 11:4 mixture of **17** and **18**, respectively. While we thus expected



that a similar oxidation of **15** should lead to the predominant formation of **13**, we were pleasantly surprised to determine that this process resulted in an apparently regiospecific conversion into the nitrone **13**, presumably associated with a favorable dihedral angle relationship between the nitrone proton at C-2 and the flanking methoxyl groups at C-3. The nitrone was then carried through to the same synthetic plan already successfully applied to *dl*-supinidine. Thus, **13** afforded unsaturated pyrrolizidine ketal **19** which was readily deprotected and reduced to the unsaturated hydroxypyrrolizidine

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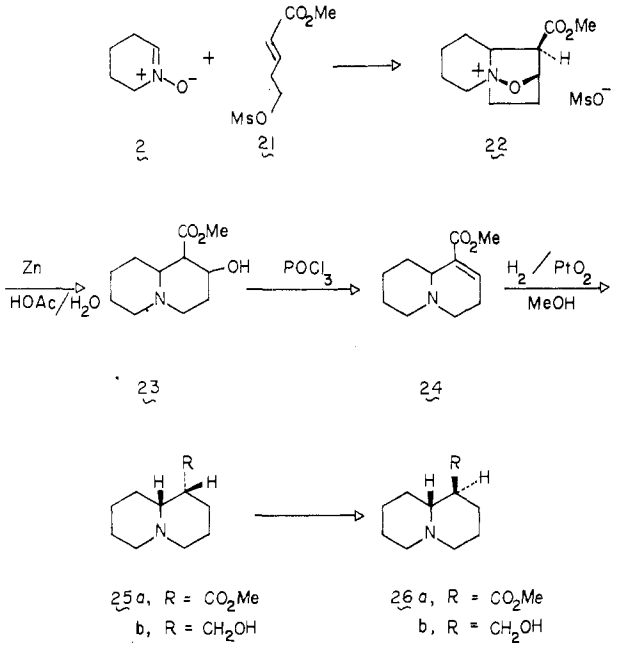
(29) An argument based on frontier orbital theory suggests that crotonates should undergo cycloaddition with nitrones in the observed direction since, in contrast with acrylates, C_α is slightly larger than C_β in the HOMO for crotonates. This reversal in the relative magnitudes of the coefficients should lead to a reversal in regiochemistry (cf. ref 11).

(30) J. J. Tufariello and G. E. Lee, unpublished observations.

(31) For the general method involved in the synthesis of *N*-ethyl-3-pyrrolidone, see N. J. Leonard, F. E. Fischer, E. Barthel, Jr., J. Figueras, Jr., and W. C. Wildman, *J. Am. Chem. Soc.*, **73**, 2371 (1951); J. F. Cavella, J. Darvoll, J. J. Dean, C. S. Franklin, and D. M. Temple, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

(32) J. J. Tufariello and P. M. Kendall, unpublished observations.

Scheme III



20, a compound previously converted to *dl*-retronecine (**6**).[33] This synthesis demonstrates the advantage of using functionally modified nitrones in organic synthesis.

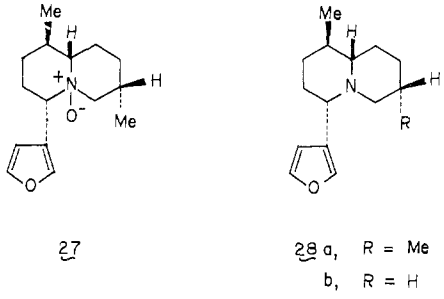
Quinolizidine Alkaloids

***dl*-Lupinine and *dl*-Epilupinine.** The successful entries into the pyrrolizidine class of alkaloids suggest a general annulation procedure applicable to the synthesis of other 1-azabicyclic alkaloids. Indeed, we penetrated[34] the Lupin family of alkaloids[35] with a stereoselective synthesis of both lupinine (**25b**) and epilupinine (**26b**) (cf. Scheme III). Thus, methyl (*E*)-5-mesyloxy-2-pentenoate (**21**) underwent reaction with 2,3,4,-5-tetrahydropyridine 1-oxide (**2**) to afford the salt **22**, formed by cycloaddition in the expected regiochemical sense, followed by an intramolecular displacement of methanesulfonate. Dehydration of the hydroxy ester **23** formed by the hydrogenolysis of the nitrogen–oxygen bond in **22** produced unsaturated ester **24**, which was reduced stereoselectively to give methyl lupinate (**25a**), and then *dl*-lupinine (**25b**) after complex metal hydride reduction. The methyl lupinate could be epimerized to yield methyl epilupinate (**26a**) and thence *dl*-epilupinine (**26b**) after reduction.

Nuphar Alkaloids

The Nuphar alkaloids[36] are found in over 100 plant species (e.g., *Nuphar lutem*, a water lily indigenous to North America). These alkaloids have been reported to possess colchicine-like antimitotic activity.[37] In addition, these compounds demonstrate important bacteriostatic and bacteriocidal properties.[38] Interestingly, the Japanese tonic senkotsu is derived from the dried roots of *N. japonicum D. C.* and is believed to possess restorative properties.[39]

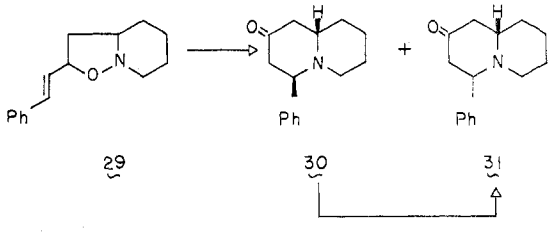
Nupharidine (**27**), obtainable from deoxynupharidine (**28a**) by oxidation, provides a challenging target be-



27 **28** a, R = Me; b, R = H

cause of the measure of stereochemical complexity incorporated. Indeed, our initial objective is 7-demethyldeoxynupharidine (**28b**), a natural product isolable from the scent gland of the Canadian beaver,[40] since this alkaloid is derivable from simple, nonfunctionalized nitrones. Although we had previously constructed the quinolizidine skeleton in our synthesis of *dl*-lupinine, it was now necessary to seek an alternative entry which could accommodate the required 4-aryl substituent.

We have shown that 4-substituted quinolizidines can be derived by the additions of nitrones (e.g., **2**) to dienes (e.g., 1-phenyl-1,3-butadiene). In principle, the addition could occur at either olefinic center. Indeed, a consideration of both stereochemical and regiochemical factors suggests the potential formation of eight isomeric monoadducts. In accord with the predictions based on a frontier orbital treatment,[41] we found[42] that the reaction afforded 5-substituted isoxazolidine **29**, as a mixture of stereoisomers, in 94% yield. Both the site selectivity and regioselectivity observed for this addition are high; moreover, the diasteromeric mixture obtained does not obscure our synthetic objective since a subsequent oxidation removes the chirality at C-2. Reductive cleavage of the N–O bond in **29**, followed by oxidation of the resultant allylic alcohol with manganese dioxide, affords, after the anticipated Michael reaction, a mixture of diastereomeric 4-phenylquinolizidin-2-ones, **30** and **31**. This mixture was subjected to equilibrating con-



ditions to produce the thermodynamically favored iso-

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(38) (a) W. Cullen, R. T. LaLonde, C. Wong, and C. Wang, *J. Pharm. Sci.*, **62**, 826 (1973); (b) K. Su, Y. Abul-Hajj, and E. Stoba, *Lloydia*, **36**, 80 (1973); (c) Y. Aleshkina, T. Il'inskaya, M. Rubinchich, and S. Vichkanova, Brit. Patent 968 042 (1964); (d) K. Beltyukoya, and L. Pastushenko, *Mikrobiol. Zh. Acad. Nauk Ukr. RSR*, **25**, 36 (1963).
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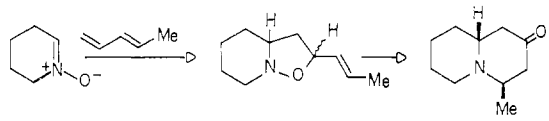
(42) J. J. Tufariello and R. C. Gatrone, *Tetrahedron Lett.*, 2753 (1978).

mer **31** in excellent yield. This compound embodies the natural configuration at C-4 (i.e., the configuration present in the Nuphar alkaloids).

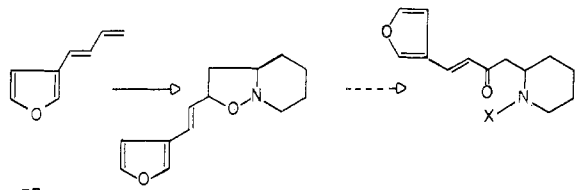
During the course of our work, a report appeared detailing the isolation and nonstereoselective synthesis of the quinolizidine base *dl*-myrtine (**32**), which incor-



2 **32**

porates an axially oriented methyl at C-5.[43] We have developed a brief, stereoselective synthesis[44] of this alkaloid based on the site-selective and regioselective addition of nitrone **2** to *trans*-piperylene. The resulting isoxazolidine was subjected to the cleavage–oxidation–Michael sequence to give *dl*-myrtine (**32**) with high stereoselectivity.[44]

Our efforts[45] toward 7-demethyldeoxynupharidine have reached the stage of the α,β-unsaturated ketone **35**. The furyl diene **33**, available by Wittig chemistry from 3-furaldehyde, undergoes the now expected mode of addition with nitrone **2**. After reductive scission of the N–O bond in **34**, the amino group is protected as a carbamate, and the resulting alcohol is oxidized to afford **35**. The completion of the synthesis awaits the

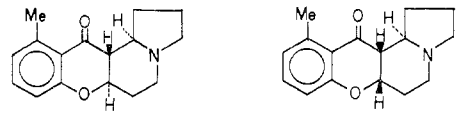


33 **34** **35**

alkylation of **35**, deprotection of the amino group with concurrent cyclization, and removal of the keto group to give **28b**.

Indolizidine Alkaloids

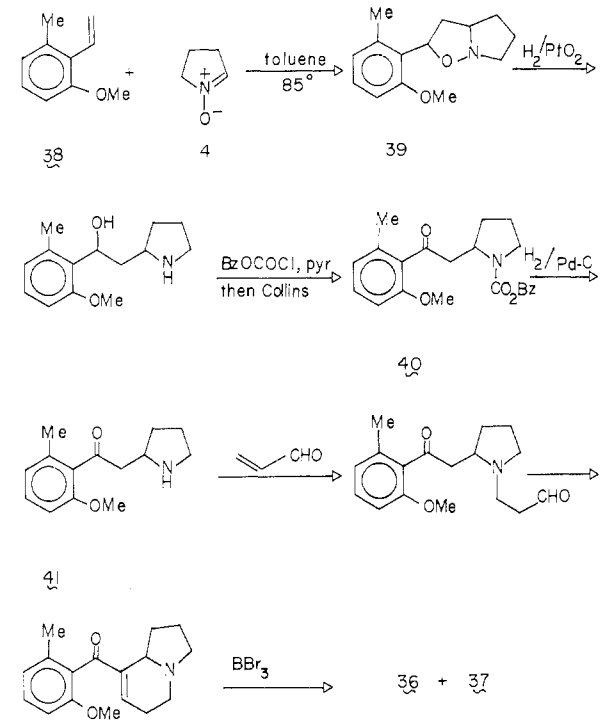
Elaeocarpine (**36**) and isoelaeocarpine (**37**) are mem-



36 **37**

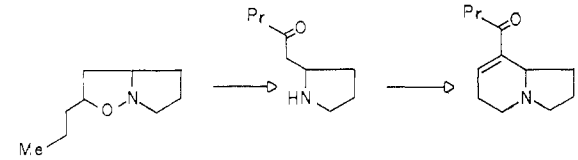
bers of a relatively new, major class of indolizidine alkaloids derived from *Elaeocarpus polydactylus* found in the rain forests of New Guinea.[46,47] A retrosynthetic analysis emphasizes the efficacy of nitrone-incorporating pathways to accommodate the presence of β-amino ketones. The initial target is obviously the β-amino ketone **41**. The synthesis is illustrated in Scheme IV.[48] The addition of **4** to the hindered styrene **38** occurs smoothly to afford isoxazolidine **39**. Through a standard sequence of steps the amino ketone **41** is produced

Scheme IV



in good overall yield. A facile Michael process involving acrolein followed by a cleavage of the methyl ether with boron tribromide[49] affords a readily separable mixture of elaeocarpine and isoelaeocarpine.[49,50]

Elaeokanine-A (**42**),[51] a structurally less complex Elaeocarpus alkaloid, has been synthesized[48] in similar fashion. The cyclization of nitrone **4** with 1-pentene gives **43** in good yield. After the usual cleavage and



43 **44** **42**

oxidation steps, the β-amino ketone **44** is converted into elaeokanine-A by the Michael-aldol strategy employed above.

Tropane Alkaloids

It appeared clear to us that intramolecular nitrone cycloadditions offered promise of access to several diverse alkaloidal classes, including those not incorporating nitrogen at a ring juncture. The tropane class of alkaloids seemed to us a good focal point in our initial efforts. These alkaloids have a long and important history in medicine. The Ebers papyrus (ca. 1550 B.C.) mentions *Hyoscyamus*, rich in tropane alkaloids, as a treatment of abdominal distress by expelling "magic of the belly".[52] One of the simplest alkaloids of the class is pseudotropine (**45**). Two independent investigations[53,54] have demonstrated that intramolecular

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(44) J. J. Tufariello, R. C. Gatrone, and C. R. Illig, work presented at Joint Chemical Congress of the American Chemical Society and the Chemical Society of Japan, Honolulu, April 2–6, 1979, ORGN 276.
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(46) S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Suares, and R. I. Willing, *Aust. J. Chem.*, **24**, 1679 (1971).
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(48) J. J. Tufariello and S. Asrof Ali, unpublished observations.
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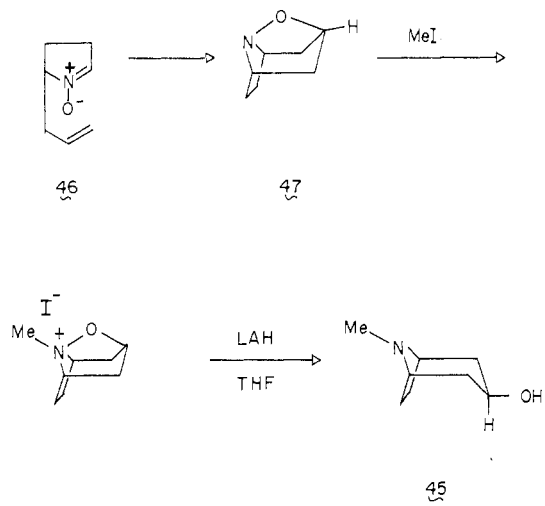
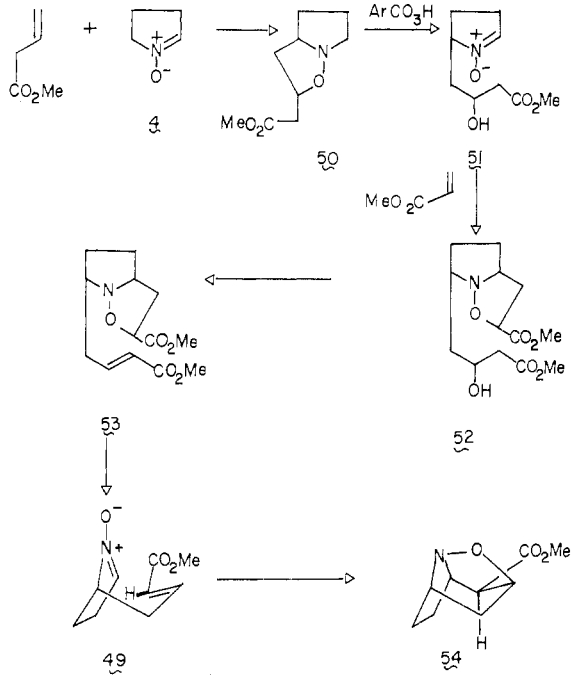
(53) J. B. Bapat, D. St. C. Black, and R. F. C. Brown, and C. Ichlov, *Aust. J. Chem.*, **25**, 2445 (1972).

Scheme V



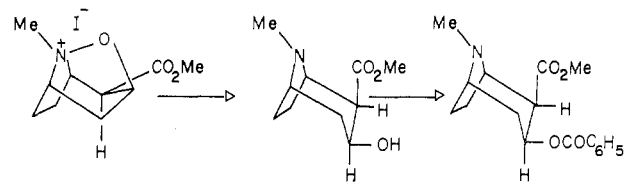
Scheme VI



nitrone cycloadditions can assemble the tropane skeleton. Cyclization of **46** was shown[54] to afford cycloadduct **47**, which was alkylated and reductively cleaved to give one of the simplest members of the tropane class of alkaloids, pseudotropine (**45**) (Scheme V).

A synthetic foray[55] in this area which highlights several advantages of nitrones in synthesis involves the chemical construction of *dl*-cocaine (**48**).[56] Retrosynthetic analysis suggests that nitrone **49** incorporates the features essential to the problem. The synthesis and cyclization of nitrone **49** are shown in Scheme VI. The addition of 1-pyrroline 1-oxide (**5**) to methyl 3-butenoate affords isoxazolidine **50** in excellent yield and with high regioselectivity. Oxidative opening of **50** with *m*-chloroperbenzoic acid in methylene chloride produces the less substituted nitrone **51** with high regioselectivity and in high yield, in contrast with earlier reports[12,57] of apparently lower yielding oxidative openings with an opposite regiochemical preference. Attempts to induce the dehydration of **51** encountered complications stemming from the free nitrone functionality. Thus, we chose to mask this sensitive grouping as its methyl acrylate cycloadduct **52** which, in turn, was converted into the unsaturated isoxazolidine **53** via the corresponding methanesulfonate. Cycloreversion of **53** to nitrone ester **49** was accompanied by concomitant intramolecular cycloaddition to give tricycloadduct **54**. The crucial stereochemical result of this process places the ester function in the desired exo orientation in **54**. This consequence stems from the trans configuration of the double bond in **49** and the maintenance of stereochemical integrity during the cycloaddition to **54**.

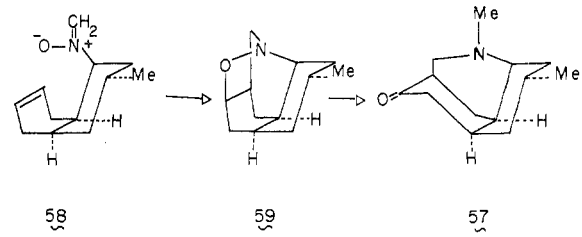
After the alkylation of **54**, the resulting methiodide **55** is subjected to reductive scission of the N–O bond, affording ecgonine methyl ester (**56**). Cocaine is



available from **56** by benzoylation.[58] While other recently reported methods[59] provide efficient entries to the tropane skeleton, the nitrone-based approach offers the advantage of the high degree of stereochemical control manifest in the introduction of the carbomethoxyl moiety. The observed regioselectivity of the peracid-induced nitrone formation from isoxazolidine **50** represents an attractive method for the symmetrical dialkylation of amines. Moreover, we have demonstrated that acrylates, and presumably other dipolarophiles, provide suitable blocking groups for the sensitive nitrone functionality. The capacity to successfully protect nitrones should greatly facilitate their involvement in organic synthesis.

dl-Luciduline

An elegantly conceived total synthesis of the Lycopodium alkaloid *dl*-luciduline (**57**) from alkenyl nitrone **58** has been reported.[60] A remarkably regioselective



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(60) (a) W. Oppolzer and M. Petrzilka, *J. Am. Chem. Soc.*, **98**, 6722 (1976); (b) W. Oppolzer and M. Petrzilka, *Helv. Chim. Acta*, 61 (1978).

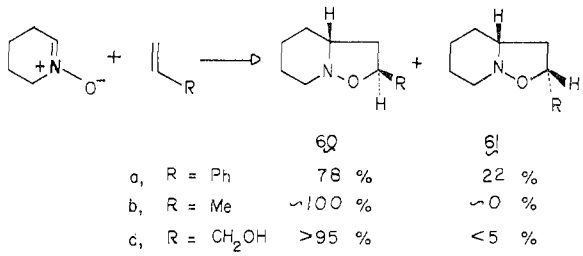
intramolecular cycloaddition provides isoxazolidine **59** and, subsequently, *dl*-luciduline. This synthesis has recently been rendered enantioselective to afford the natural configuration of (+)-luciduline.[60b] A feature that makes this synthesis particularly attractive is the incorporation of another cycloaddition variant, the Diels–Alder reaction, in the construction of the gross skeletal features of **58** and in making provision for the configuration of the cis-fused decalenyl system.

Stereochemistry

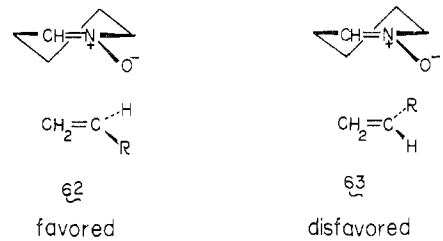
While sufficient attention has been devoted to the regiochemical aspects of nitrone cycloadditions to permit rational predictions to be made, the stereochemical aspects of these additions have received somewhat less attention. Since the stereochemical features of the intramolecular cycloadditions are often complicated by constraints imposed by entropic factors,[3] the essential stereochemical features of nitrone–alkene cycloadditions should be most easily discerned by an examination of intermolecular processes.[1]

Acyclic nitrones, such as *C*-phenyl-*N*-methylnitrone, react with alkenes to exhibit a range of stereoselectivities. For example, this nitrone adds to styrene to afford a mixture of diastereomeric isoxazolidines in a 2:1 ratio, respectively.[61] While *C*,*N*-diphenylnitrone reacts with methyl acrylate to produce a 57:43 ratio of the corresponding diastereomeric adducts, it reacts with acrylonitrile with high stereoselectivity.[28] The reaction of *C*-phenyl-*N*-methylnitrone with cyclohexene has been shown[62] to afford two adducts in a 5:4 ratio, presumably the result of cis ⇄ trans isomerization of the starting nitrone, a feature which complicates the interpretation of results from cycloadditions involving acyclic nitrones.

Our own efforts have concentrated on the stereochemical consequences related to the cycloaddition reactions of cyclic nitrones.[63] In particular, we have shown that nitrone **2** reacts with a range of monosubstituted alkenes to give a mixture of diastereomeric adducts (i.e., **60** and **61**). Clearly, that adduct predominates which arises (using Diels–Alder terminology) from an exo transition state (i.e., **62**); however, those



		60	**61**
a,	R = Ph	78 %	22 %
b,	R = Me	~100 %	~0 %
c,	R = CH_2OH	>95 %	<5 %
d,	R = CO_2Me	82 %	18 %



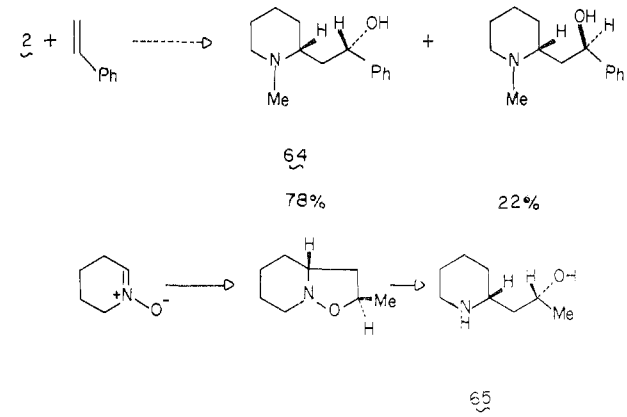
62 favored **63** disfavored

(61) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, **101**, 2548 (1968).
(62) L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. B*, 1728 (1971).
(63) J. J. Tufariello and Sk. Asrof Ali, *Tetrahedron Lett.*, 4647 (1978).

dipolarophiles capable of favorable secondary orbital interactions show some tendency to give results expected from the passage through endo transition states (i.e., **63**).

A recent study suggests that nitronic esters add to certain α,β-diactivated alkenes (e.g., dimethyl maleate) with high stereoselectivities to produce endo adducts, presumably due to the stabilization of the endo transition states by secondary orbital effects.[64-66] In contrast, the cycloadditions involving nitronic esters and activated monosubstituted olefinic dipolarophiles have been shown[65] either to proceed through exo transition states (e.g., substituted styrenes) or to exhibit random stereochemical results (e.g., acrylonitrile).

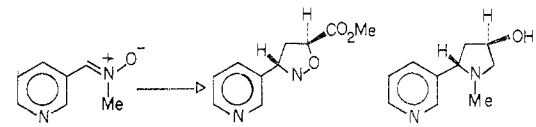
We have used the stereochemical tendencies elucidated for the cycloadditions of cyclic nitrones to synthesize *dl*-allosedamine (**64**) with moderate stereoselectivity and *dl*-sedridine (**65**) with very high stereoselectivity.[63]



64 78% 22%

65

The tendency of cyclic nitrones to undergo addition via exo oriented transition states is further illustrated by the cycloaddition of nitrone **66** with methyl acrylate to give isoxazolidine **67**, which after hydrogenolysis and



66 **67** **68**

concomitant lactamization followed by a straightforward inversion procedure provides hydroxycotinine (**68**), a nicotine metabolite found in the urine of smokers.[67]

Although not directed toward an alkaloidal system, we note that nitrones, as well as nitrile oxides, have been effectively employed in the synthesis of biotin.[5c] While this Account has gained focus from the dipolar cycloaddition reactions of nitrones, clearly other aspects of nitrone chemistry can be useful in synthesis.[1-3,15] Thus, a synthesis[68] of desdanine takes advantage of the ability of the methyl group of 2-methyl-1-pyrroline 1-oxide to be deprotonated and undergo condensation with carbonyl compounds,[68-71] while investigations of

(64) R. Grêe and R. Carrié, *Tetrahedron Lett.*, 4117 (1971); M. Joucla, F. Tonnard, D. Grêe, and J. Hamlin, *J. Chem. Res. (S)* (7) 240 (1978).
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(66) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
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(68) W. Martin and W. Durckheimer, *Tetrahedron Lett.*, 1459 (1973).

the rich chemistry of α-chloro nitrones have resulted in the discovery of numerous synthetically significant transformations.[72]

Conclusion

We have attempted to show the development of a general methodology applicable to the synthesis of a variety of alkaloidal classes (e.g., the pyrrolizidine, quinolizidine, indolizidine, lycopodium, and tropane classes). The cycloadditions discussed are normally well-behaved,[73] efficient reactions. The inherent features of carbon–carbon bond formation, oxygen transfer, and nitrogen incorporation have been joined by the high site selectivities, regioselectivities, and stereoselectivities often observed in nitrone–alkene cycloadditions to render these reactions powerful weapons in the arsenal of the organic chemist. Indeed, it is our firm conviction that such processes will play an ever increasing role in the expansionary phase that is currently underway in organic synthesis.

Any success achieved in the program described herein must be attributed substantially to my numerous productive and stimulating collaborators. Thanks for material support go to the National Institutes of Health (GM 25303 and CA 14611) and the Research Foundation of the State University of New York.

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(71) J. J. Tufariello and E. J. Trybulski, unpublished observations.
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(73) However, see J. J. Tufariello and E. J. Trybulski, *J. Org. Chem.*, **39**, 3378 (1974); E. Gossinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, **58**, 96 (1975).

Role of Activation Volume in the Elucidation of Reaction Mechanisms in Octahedral Coordination Complexes

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The effect of pressure on the rate of a chemical reaction in solution, which can be attributed to a volume change occurring in the activation step, has been gaining recognition as an aid in mechanistic elucidation. The existence of a correlation between the main mechanistic features of a reaction and the activation volume is now widely accepted. Extensive studies of organic reactions using this technique have appeared.[2] However, applications of the effect of pressure in the area of inorganic reaction mechanisms are still limited, though growing steadily.

Advances in modern high-pressure techniques and equipment have made the measurement of the effect of pressure on reaction rate relatively simple. Activation enthalpies and entropies obtained from the effect of temperature on reaction rates can now be supplemented by activation volumes obtained from the pressure dependence of reaction rates. The interpretation of mechanism based on entropy change requires a structural concept involving inferred changes in both energy and nuclear position; volume change is based on changes in nuclear position only, and should therefore be inherently simpler to intercept.

Geoffrey A. Lawrance was born in Ipswich, Australia, in 1948. He received his B.Sc. and Ph.D. degrees from the University of Queensland, and a Dip.Ed. from the University of Melbourne. He held posts as Research Fellow at the University of Stirling (Scotland) and Senior Tutor and Lecturer at the University of Melbourne before taking up his present position as Research Fellow in the Research School of Chemistry at the Australian National University in 1978.

Donald R. Stranks was born in Melbourne in 1929, and received M.Sc. and Ph.D. degrees from the University of Melbourne. He was Professor of Inorganic Chemistry at the University of Adelaide and then at the University of Melbourne before returning to Adelaide as Vice-Chancellor in 1977.

The *activation volume* ($\Delta\bar{V}^{\ddagger}$) for the generalized reaction

$$aA + bB + \ldots \rightleftarrows T^{\ddagger} \rightleftarrows cC + dD + \ldots \quad (1)$$

can be defined as[3]

$$\Delta\bar{V}^{\ddagger} = -RT(\partial \ln k_p/\partial P)_T \quad (2)$$

which can also be written in terms of partial molar volumes ($\bar{V}_i$) as

$$\Delta\bar{V}^{\ddagger} = \bar{V}_{T\ddagger} - a\bar{V}_A - b\bar{V}_B - \ldots = \bar{V}_{T\ddagger} - \sum_A a\bar{V}_A \quad (3)$$

The *reaction volume* ($\Delta\bar{V}^0$), or partial molar volume change for the reaction, can be expressed as

$$\Delta\bar{V}^{\circ} = -RT(\partial \ln K/\partial P)_T \quad (4)$$

or

$$\Delta\bar{V}^{\circ} = (c\bar{V}_C + d\bar{V}_D + \ldots) - (a\bar{V}_A + b\bar{V}_B + \ldots) \quad (5)$$

$$= \sum \bar{V}_{\text{products}} - \sum \bar{V}_{\text{reactants}} \quad (6)$$

For convenience, it has become common practice to delete the bar over the volume symbol used to indicate partiality and, subsequently, *activation volume* will be symbolized by $\Delta V^{\ddagger}$ and *reaction volume* by ΔV^0. The activation volume can be calculated only from the effect of pressure on the rate constant and application of eq 2. The reaction volume can be determined by dilato-

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(2) T. Asano and W. J. le Noble, *Chem. Rev.*, **78**, 407 (1978).
(3) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

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