The Regiochemistry and Stereochemistry of 1,3-Dipolar Cycloaddition of a Cyclic Nitrone

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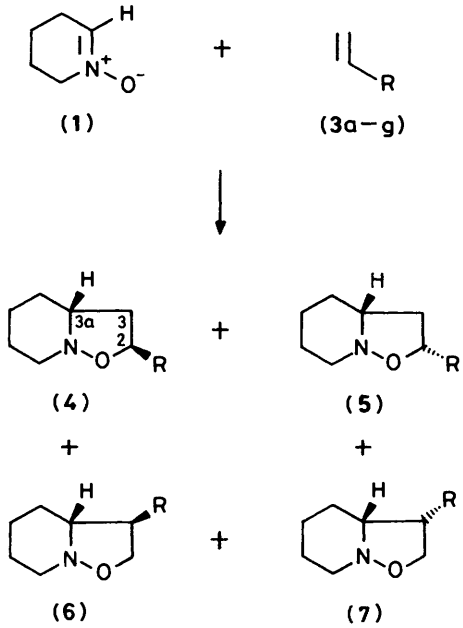
A study of the regiochemical and stereochemical behaviour of the 1,3-dipolar cycloaddition of a series of alkenes with 2,3,4,5-tetrahydropyridine 1-oxide has been carried out. The high degree of both regiochemical and stereochemical control observed in these reactions has been explained in terms of maximum overlap of frontier orbitals, repulsive steric encumbrance, and attractive secondary orbital interaction in the transition state. Most monosubstituted and 1,1-disubstituted alkenes gave 2-substituted cycloadducts. As the electron affinity of the monosubstituted alkene increases, an increasing tendency towards formation of the regioisomeric 3-substituted cycloadduct is encountered. 1,2-Disubstituted alkenes undergo cycloadditions to afford cycloadducts with electron-withdrawing substituents always in the C-3 position of the cycloadducts. Significant secondary orbital interaction is observed with the non-conjugated hydroxymethyl substituent.

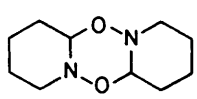
1,3-Dipolar cycloadditions of nitrones with alkenes are the best chemical templates for constructing isoxazolidines in high yields.[1] The presence of two heteroatoms in the nitrone functionality and its nearly singular capability to incorporate several stereochemical centres in a single step has made nitrone cycloadditions specially attractive for the synthesis of several natural products.[2] The regiochemical aspects of inter-[3,4] and intra-molecular[5,6] additions involving both cyclic and acyclic nitrones have been explored in some detail. However, the stereochemical details of these cycloadditions have been examined only to a limited extent because of the difficulty associated with unambiguous assignment of adduct configurations.[7,8] Perturbation MO theory is remarkably successful in explaining regioselectivity and reactivity phenomena in dipolar cycloadditions.[4,9–13] According to Sustman's classification,[10] the nitrone functionality is a type II dipole where both HOMO–LUMO interactions contribute to the stabilization of the transition state. Steric factors and secondary orbital interactions usually dictate the stereochemical outcome of the cycloadditions.[7,11,12]

Even though the synthetic applications of nitrone cycloaddition are a recent development, they have already had a significant impact on the synthesis of natural products.[2] The regio- and stereo-chemical integrity of these additions hold the key to the efficiency of certain total syntheses. Here we report, in detail, the regio- and stereo-chemical features associated with the cycloaddition of cyclic nitrone, 2,3,4,5-tetrahydropyridine 1-oxide (**1**) onto several mono-, 1,1-di-, and 1,2-di-substituted alkenes. The nitrone (**1**) was chosen because of its importance in the synthesis of piperidine alkaloids, which are widespread in nature.



a; R = Me
b; R = OEt
c; R = CH_2OH
d; R = Ph
e; R = CO_2Me
f: R = CN
g; R = CHO
h; R = CH_2OSO_2Me

Scheme 1.



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Results and Discussion

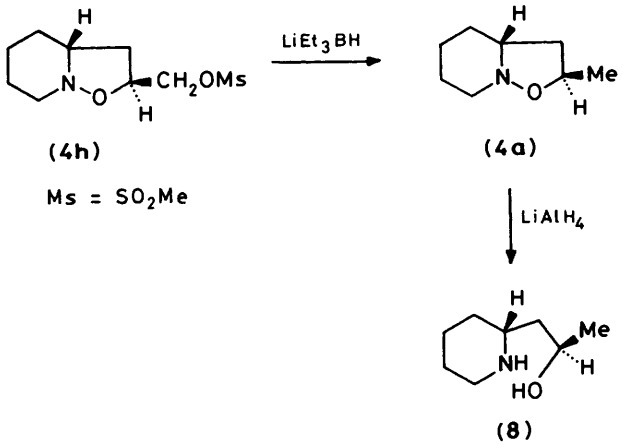
Initially, we chose to investigate the addition of the nitrone (**1**) onto several monosubstituted alkenes (Scheme 1). All reactions were carried out under kinetically controlled conditions. Most often, an excess of alkene and protic solvents were employed in order to suppress the formation of the nitrone dimer[14] (**2**). Regio- and stereo-chemical details of these additions along with the reaction temperature, solvent, isolated yield, and composition of isomeric cycloadducts are given in Table 1.

Addition of the nitrone (**1**) to propene gave a single adduct (**4a**). The regio- and stereo-chemical outcome of this addition was confirmed by reducing (**4a**) with lithium aluminium hydride to give naturally occurring alkaloid (±)-sedridine (**8**) (Scheme 2).[7] Ethyl vinyl ether appears to undergo regioselective addition[14] to give (**4b**) and (**5b**) in a 93:7 ratio, as determined by the integration of C-2 protons at δ 5.18 (1 H, dd, *J* 3.0 and 10.0 Hz) and 5.07 (1 H, dd, *J* 4.0 and 6.0 Hz). The cycloadducts (**4b**) and

Table 1. Regio- and stereo-chemistry of cycloadditions of the nitrone (**1**) with monosubstituted alkenes

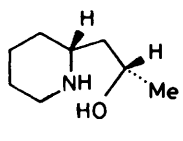
Alkene (3)	Temp (°C)	Reaction time (h)	Solvent	% Composition of adducts (4)	(5)	(6)	(7)	Isolated yield (%)
a	110	4	Toluene	100	0	0	0	53
b	40	12	EtOH	93	7	0	0	67
c	80	5	Toluene	83	17	0	0	84
d	110	5	Toluene	78	22	0	0	92
e	0	0.2	CH_2Cl_2	69	15	10	6	96
f	25	0.5	CH_2Cl_2	61	20	13	6	92[a]
g	25	0.2	CH_2Cl_2	3	5	24	68	96[b]

[a] Isolated yield of the corresponding carboxymethyl derivatives (**4e**)—(**7e**). [b] Isolated yield of the corresponding alcohols (**4c**)—(**7c**).



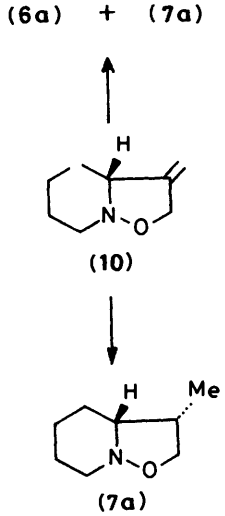
Scheme 2.

(**5b**) were found to be unstable, extensive decomposition occurring above 70 °C. The reaction of allyl alcohol with (**1**) produced a non-separable mixture of 2-substituted adducts, (**4c**) and (**5c**), in ratio of 83:17. The stereochemical analysis of this mixture of isomers was accomplished by methanesulphonylation followed by chromatographic separation of the methanesulphonates (**4h**) and (**5h**). The purified methanesulphonates were converted into (**4a**) and (**5a**) by Super-hydride induced S_N2 displacement of the methanesulphonates function by hydride ion (Scheme 2).[7,15] The methyl protons at C-2 of (**4a**) and (**5a**) appeared at δ 1.26 (d, *J* 6.0 Hz) and 1.33 (d, *J* 6.4 Hz) respectively. Conversion of (**5a**) into naturally occurring alkaloid (±)-allosedridine (**9**) assures the assigned stereochemistry of the minor isomer (**5c**).



The reactions of the nitrone (**1**) with styrene and methyl acrylate have been reported earlier.[7] The result of these additions are also included in Table 1. While styrene appears to undergo regioselective addition to (**1**), methyl acrylate, acrylonitrile, and acrylaldehyde afforded a regioisomeric mixture of all four possible adducts in each case. The ^1H n.m.r. spectrum of the crude reaction products from acrylonitrile was not helpful in assigning the stereochemistry of the diastereoisomers. Complete stereochemical analysis was carried out by conversion of the mixture of adducts (**4f**)—(**7f**) into the corresponding methanesulphonates (**4h**)—(**7h**) by passing anhydrous hydrogen chloride into a cold solution of the nitriles in anhydrous methanol,[16] reduction of the resultant CO_2Me group with lithium aluminium hydride, followed by methanesulphonylation. The methanesulphonates were separated into two fractions by chromatography. While the less polar fraction contained a mixture of (**5h**) and (**7h**), the more polar fraction was a non-separable mixture of (**4h**) and (**6h**). The methyl singlets of (**4h**) and (**5h**) appeared at δ 3.10 and those of (**6h**) and (**7h**) appeared at δ 3.06 and 3.04, respectively. The absence of any overlapping signals in that region allowed the determination of the distribution of the diastereoisomers (Table 1).

A reversal in the regioselection occurred when acrylaldehyde was allowed to react with the nitrone (**1**). A mixture of isomers (**4g**)—(**7g**) was obtained in an approximate ratio of 3:5:24:68. The crude reaction mixture was reduced with sodium borohydride and then methanesulphonylated. The methanesulphonates were separated by chromatography and the stereochemical analysis is recorded in Table 1. The assignment of *endo* orientation of the C-3 substituent in the major isomer (**7g**) or (**7h**) is based on the results of hydrogenation of adduct (**10**) derived[17] from allene and the nitrone (**1**) (Scheme 3). While the



Scheme 3.

di-imide reduction led to a mixture of compounds (**6a**) and (**7a**), the hydrogenation over Pd–C afforded a single product (**7a**). The hydrogenation is assumed to take place from the less hindered side containing the bridgehead hydrogen. The

Table 2. Stereochemistry of cycloadditions of the nitrone (**1**) with 1,1-disubstituted alkenes

Alkene (**11**)	Temp (°C)	Reaction time (h)	Solvent	% Composition of adducts (**12**)	% Composition of adducts (**13**)	Isolated yield (%)
a	25	0.4	CH_2Cl_2	100	0	94
b	25	1.5	CH_2Cl_2	96	4	86
c	95	5	Toluene	85	15	77
d	95	2	Toluene	83	17	66
e	95	1.5	Toluene	70	30	55
f	95	1.5	Toluene	67	33	58
g	105	1	Toluene	58	42	71

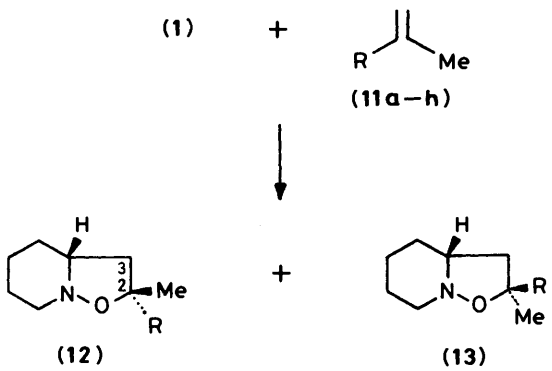
Table 3. Stereochemistry of cycloadditions of the nitrone (**1**) with 1,2-disubstituted alkenes

Alkene	Temp (°C)	Reaction time (h)	Solvent	% Composition[a] of adducts		Isolated yield (%)
(**14a**)	35	8	CH_2Cl_2	(**16a**) (100)	(**17a**) (0)	82
(**14b**)	55	2	Toluene	(**16b**) (87)	(**17b**) (13)	79
(**14c**)	25	2	CH_2Cl_2	(**16c**) (100)	(**17c**) (0)	87
(**14d**)	40	1	CH_2Cl_2	(**16d**) (90)	(**17d**) (10)	94
(**14e**)	25	2	CH_2Cl_2	(**16e**) (60)	(**17e**) (40)	89
(**15a**)	25	2	CH_2Cl_2	(**18a**) (84)	(**19a**) (16)	93
(**15b**)	25	0.1	CH_2Cl_2	(**18b**) (81)	(**19b**) (19)	98

[a] Compositions are shown in parentheses.

methanesulphonates (**6h**) and (**7h**) were converted into the corresponding methyl derivatives (**6a**) and (**7a**), respectively, by Super-hydride reduction. The methyl doublets of compounds (**6a**) and (**7a**) appeared, without any overlap, at δ 1.08 and 1.00 respectively.

Next, we pursued the cycloaddition of nitrone (**1**) with a number of 1,1-disubstituted alkenes (Scheme 4). The results of



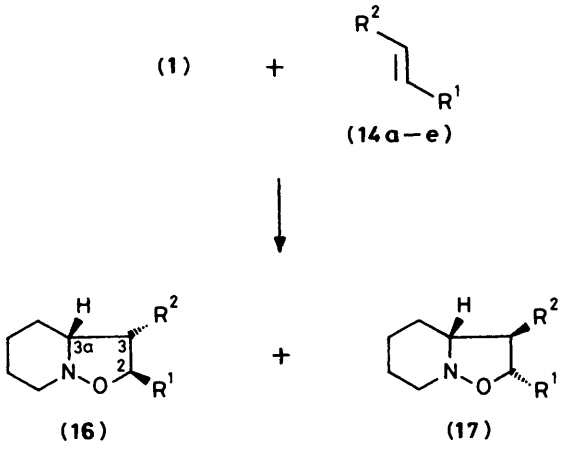
a; R = CHO
b; R = CO_2Me
c; R = CH_2OH
d; R = CH_2OCOMe
e; R = $CH_2OSiBu^t(Me)_2$
f; R = CH_2OTHP
g; R = Ph
h; R = OMe
i; R = CH_2OSO_2Me

Scheme 4.

our stereochemical analysis are recorded in Table 2. Methacrylaldehyde underwent stereoselective addition onto the nitrone (**1**) to afford a single adduct (**12a**). For steric reasons and favourable secondary orbital interactions,[11,12] the smaller aldehyde group is assumed to have *endo* orientation in (**12a**). The absence of the diastereoisomer (**13a**) was confirmed by reduction of the crude reaction product with sodium borohydride followed by methanesulphonylation to give the single methanesulphonate (**12i**). The cycloaddition of (**1**) with methyl methacrylate gave a mixture of adducts (**12b**) and (**13b**) in a ratio of 96:4, respectively. This was determined by its conversion into a separable mixture of methanesulphonates (**12i**) and (**13i**). However, highly stereoselective formation of the isomer (**13**) was required for the proposed alkaloid synthesis. To our dismay, the addition of methylallyl alcohol (**11c**) and its dimethyl-t-butylsilyl ether (**11e**), and tetrahydropyranyl ether (**11f**) onto (**1**) afforded, respectively, (**12c**), (**12e**), and (**12f**) as the major isomers (Table 2). The ratio of the adducts in each case was determined by the chemical transformations to a separable mixture of methanesulphonates (**12i**) and (**13i**). The crude adducts (**12d**) and (**13d**) from methylallyl acetate (**11d**) was formed in a ratio of 83:17. The major isomer (**12d**) is assigned the configuration with an *endo* acetoxymethyl group and was confirmed by the conversion of (**12a**) into (**12d**) by sodium borohydride reduction followed by acetylation.

The reaction of α-methylstyrene (**11g**) with (**1**) afforded a separable mixture of the adducts (**12g**) and (**13g**) in a ratio of 58:42. As a result of favourable secondary orbital interaction, as demonstrated in the case of styrene, the major isomer is believed to have the phenyl group in *endo* orientation. The addition of 2-methoxypropene failed to give any identifiable products, the reaction being too slow at 70 °C. At a higher temperature the nitrone (**1**) was consumed but the ^1H n.m.r. spectrum of the crude reaction mixture was too complex, presumably owing to extensive decomposition of the cycloadducts.[18]

Finally, we studied the cycloaddition behaviour of the nitrone (**1**) with several 1,2-disubstituted alkenes. The stereochemical analyses of these additions are summarized in Table 3. The nitrone (**1**) with *trans*-cinnamaldehyde (**14a**) afforded the adduct (**16a**) stereoselectively. This was confirmed by reduction of the crude reaction product with sodium borohydride to give the single alcohol (**16f**). The addition of *trans*-methyl cinnamate (**14b**) gave a separable mixture of adducts (**16b**) and (**17b**) in a

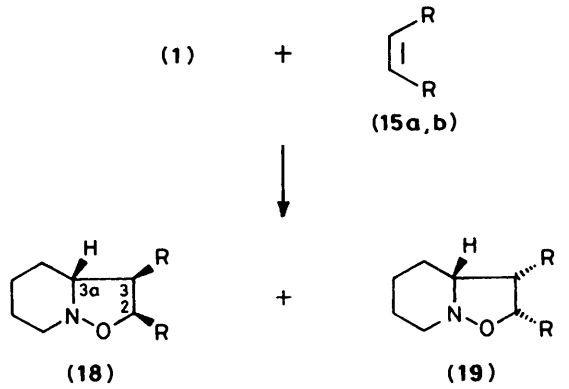


a; R^1 = Ph; R^2 = CHO
b; R^1 = Ph; R^2 = CO_2Me
c; R^1 = Me; R^2 = CHO
d; R^1 = Me; R^2 = CO_2Me
e; R^1 = R^2 = CO_2Me
f; R^1 = Ph; R^2 = CH_2OH
g; R^1 = Me; R^2 = CH_2OH
h; R^1 = Me; R^2 = CH_2OSO_2Me
i; R^1 = R^2 = Me
j; R^1 = R^2 = CH_2OH
k; R^1 = R^2 = CH_2OSO_2Me

Scheme 5.

87:13 ratio. The crude reaction mixture, on reduction with lithium aluminium hydride, afforded a mixture of alcohols (**16f**) and (**17f**) as revealed by the presence of two doublets at δ 5.08 (*J* 3.5 Hz) and 4.78 (*J* 5.5 Hz) due to the C-2 protons of the alcohols (**16f**) and (**17f**), respectively. *endo* Orientation was assigned to the R^2 group at C-3 in the major isomer (**16a**, **b**) because of the significant tendency of the aldehyde (R^2 = CHO) and methoxycarbonyl (R^2 = CO_2Me) group to manifest favourable secondary orbital interaction.[8a,e]

While the reaction of the nitrone (**1**) with *trans*-crotonaldehyde (**14c**) gave a single adduct (**16c**), a mixture of adducts (**16d**) and (**17d**) was obtained in a ratio of 9:1 from the addition of methyl crotonate. The C-2 protons in (**16d**) and (**17d**) appeared as quintets at δ 4.53 (*J* 6.0 Hz) and 4.36 (*J* 6.5 Hz) respectively. The coupling constants were indicative of their *trans* relationship in each case. The major adduct[8a] has been proved to have the stereochemistry as depicted in (**16d**). Studies of the stereochemistry of nitrone–crotonate cycloadditions have amply demonstrated a significant tendency of the methoxycarbonyl group to manifest secondary orbital interaction.[8a,e] Addition of dimethyl fumarate afforded two separable adducts (**16e**) and (**17e**) (6:4 respectively). The major adduct (**16e**) was converted into (**16i**) by reduction with lithium aluminium hydride, methanesulphonylation followed by Super-hydride induced displacement of the methanesulphonate function. The stereochemistries of adducts (**16c**)—(**16e**) were confirmed by their chemical transformation to (**16i**). In a similar manner, compound (**17e**) was converted into compound (**17i**) for comparison purposes. Dimethyl maleate and maleic anhydride afforded compounds (**18a**) and (**18b**) respectively, as the major adduct with *exo* orientation of the substituents (Scheme 6). This is in line with the favoured *exo* mode of attack observed in the case of methyl acrylate, where favourable secondary orbital interaction is not large enough to over-ride the steric factor present in the *endo* transition state. Inspection of molecular models revealed that the protons at C-3 and C-3a form dihedral angles of *ca.* 90° in compound (**18b**). This is indeed demonstrated in the ^1H n.m.r. spectrum which shows the 3-H as



a; R = CO_2Me
b; R, R = $(CO)_2O$
c; R = CH_2OH
d; R = CH_2OSO_2Me
e; R = Me

Scheme 6.

a doublet ($J_{2,3}$ 7.8 Hz) at δ 3.45. Irradiation of the signal for the 2-H doublet ($J_{2,3}$ 7.8 Hz) at δ 5.01 caused the doublet at δ 3.45 to collapse into a singlet. Irradiation of the 3a-H at δ 3.75 had no effect on the 3-H doublet. The ratio of the maleic anhydride and dimethyl maleate adducts were determined by the conversion of the reaction mixtures into the dihydroxy compounds (**18c**) and (**19c**) and integrating the C-2 proton multiplets at δ 4.26 and 4.50 respectively. Irradiation of the CH_2O protons at δ 3.86 caused these multiplets to collapse into two doublets as expected. The non-separable mixture of these dihydroxy compounds was dimethanesulphonated and separated by chromatography to give (**18d**) and (**19d**). While (**18d**) was converted into (**18e**) in good yield, (**19d**) failed to give (**19e**), presumably due to steric encumbrance inherent in the *endo* oriented dimethanesulphonates.

All reactions were run under conditions which would reflect kinetic rather than thermodynamic factors. The cycloaddition products are, in principle, capable of undergoing cycloreversion to the nitrone. However, cycloaddition is reversible only at elevated temperatures. Such thermal reversibility has been noted in the literature[8c,d] only in few additions involving nitrones and electron-deficient monosubstituted alkenes. 5,5-Dimethylpyrroline *N*-oxide and ethyl acrylate[8d] afforded the 2-substituted adduct at room temperature (24 h) and the 3-substituted isomer at 100 °C (4 days). The same nitrone gave the 2-substituted adduct with acrylonitrile[8c] at 25 °C (54 h) and a mixture of regioisomers at 77 °C (96 h). It should be noted that most of the cycloadditions were carried out for much shorter periods at low temperatures. Maleic anhydride (or acrylaldehyde) at two different temperatures (0 and 25 °C) gave a similar ratio of adducts. When several purified adducts were subjected to similar reaction conditions to those under which they were prepared, they remained unchanged. For example, when the purified isomer (**12g**) (0.5 mmol) [or (**13g**)] was heated in toluene (5 ml) and α-methylstyrene (3 mmol) for 1 h at 105 °C, the adduct (**12g**) [or (**13g**)] was recovered unchanged and thermal reversibility to the nitrone was not observed.

The results discussed above are in general agreement with the frontier orbital treatment of the nitrone 1,3-dipolar cycloadditions.[4,9–13] In the case of electron-rich monosubstituted alkanes both HOMO–LUMO contributions prefer the formation of 2-substituted regioisomers by uniting the larger terminal coefficients in the transition state (Figure 1).[11,12] As the ionization potential and the electron affinity of the alkene increase (*i.e.* as the HOMO–LUMO levels decrease in energy)

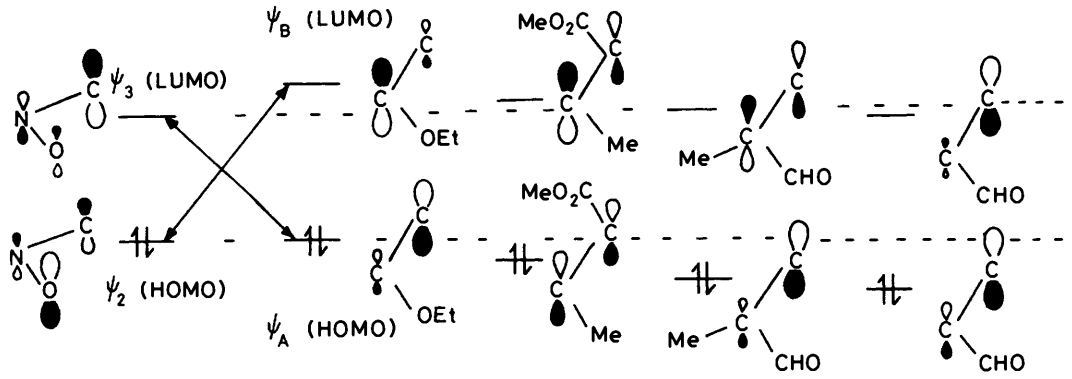


Figure 1. A qualitative representaton of the energies and orbital coefficients of nitrone and alkenes

there is an increasing tendency towards the producton of a regioisomeric mixture of adducts.[3b,13,19]

Nitrone cycloaddition is a type II process[10] where both HOMO–LUMO interactions can contribute effectively to the stabilization of the transition state. The additions of methylallyl alcohol and its derivatives (**11d**—**f**) are regioselective and gave only 2-substituted adducts as predicted by the frontier orbital theory. The two substituents have a similar effect on the frontier orbital coefficients at both carbons in the alkene. However, in 1,1-disubstituted alkenes like methacrylaldehyde, and methyl methacrylate with one electron-withdrawing substituent, the LUMO coefficients are nearly the same on both carbon atoms. Then the regiochemical outcome is determined by nitrone (LUMO)–alkene (HOMO) interaction, which favours the transition state leading to the 2-substituted regioisomer. Likewise, the regiochemical outcome of the reactions of methyl crotonate (and methyl cinnamate *etc.*) with the nitrone (**1**) can be qualitatively explained in terms of maximum orbital overlap. Perturbation MO theory relates to an early point on the reaction co-ordinate and accounts for a fraction of the activation energy. The large negative entropies of activation for cycloadditions suggest the dominance of steric encumbrance in deterring the formation of the adduct *via* an *endo* transition state.[12] However, conjugating substituents can overcome this potential difficulty by favourable secondary orbital interaction between the orbitals of the nitrogen atom of the nitrone and the *cis* conjugated double bond of the substituent attached to the alkene.[12] Unexpected formation of the major adducts (**18a**, **b**) *via* the *exo* transition state presumably suggests the dominance of steric factors over secondary orbital interaction in the transition states. Significant preference for the *endo* approach observed in the addition of even the dimethyl-t-butylsilyl ether of methylallyl alcohol is probably due to the stabilizing interaction between the nitrogen atom of the nitrone LUMO with the oxygen lone pair of the alkene (Figure 2). Similar stabilizing interaction has been reported earlier.[20] However, this proposed rationale needs further experimental and theoretical justification.

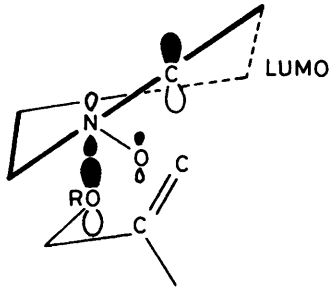


Figure 2.

Even though nitrones, both cyclic and acyclic, show similar regiochemical behaviour, their stereochemical behaviour in the cycloaddition is somewhat different.[7] Acyclic nitrones can undergo $E \rightleftharpoons Z$ isomerization prior to cycloaddition.[8a,21] These isomers not only differ in their reaction rate but also complicate the stereochemical outcome.[21] The cyclic nitrone which can exist only in the *E* form, because of structural constraints, shows remarkable regio- and stereo-selectivity. In this work we were able to confirm the configurations of the dipolar cycloaddition products through lengthy chemical conversions. These results may be extrapolated in predicting the addition reactions of related cyclic nitrones. The regio- and stereo-chemical integrity observed in our study would indeed be helpful in incorporating multiple stereocentres in the synthesis of natural products.

Experimental

All m.p.s are uncorrected. Elemental analyses were performed on a Carlo-Erba Elemental analyser 1106. I.r. spectra were recorded on a Perkin-Elmer instrument model 237B, and are reported in wavenumbers (cm^{-1}). ^1H N.m.r. spectra were measured in $CDCl_3$ with TMS as internal standard, on a Varian XL-200 n.m.r. spectrometer operating in the pulse-FT mode. 70 eV E.i. mass spectra were recorded on a Ribermag GC-MS system, R-10-10 with Quadrupole mass filter and Riber 400 acquisition system. Silica gel chromatographic separations were performed with silica gel 60 F_{254} (Fluka AG). T.l.c. cards silica gel, aluminium backed plates (Fluka AG, layer thickness 0.2 mm) were used to determine the appropriate solvent system for elution. Reagent grade dichloromethane was passed through active alumina. All solvents were Reagent Grade. Toluene and THF were sodium-dried and distilled prior to use. All the liquid alkenes and the *N*-hydroxypiperidine were distilled and maleic anhydride and dimethyl fumarate were recrystallized before use. Cycloadditions were conducted under a positive atmosphere of nitrogen.

2,3,4,5-*Tetrahydropyridine* 1-*Oxide* (**1**).—To a stirring solution of *N*-hydroxypiperidine (5.05 g, 50 mmol) in CH_2Cl_2 (200 ml) at 0 °C under N_2 was added yellow HgO (31.2 g, 150 mmol) in three portions over a period of 10 min. The HgO was converted into a greyish mixture (presumably consisting of Hg and excess HgO) within minutes after addition. The reaction mixture was stirred for an additional 0.5 h at 0 °C, filtered through a bed of Celite and dry $MgSO_4$, and the bed washed with cold CH_2Cl_2. The nitrone solution was concentrated under reduced pressure at 0 °C to 200 ml and was kept in the freezer to minimize dimerization. The information of the nitrone was assumed to be quantitative in the percentage yield calculations for the subsequent cycloadditions. When the reactions were run in

solvents other than CH_2Cl_2, the required amount of nitrone solution was evaporated under reduced pressure at 0 °C to dryness and the residue dissolved in cold solvent (25 ml) and used immediately.

In all the cycloadditions 5 mmol of nitrone in 25 ml of solvent was treated with the alkene. The alkenes used, with the amount in mmol written in parentheses, are as follows: allyl alcohol (25), acrylonitrile (15), acryladehyde (10), methacrylaldehyde (10), methyl methacrylate (10), methylallyl alcohol (30), methylallyl acetate (17), tetrahydropyranyl ether (10), dimethyl-t-butylsilyl ether (10), α-methylstyrene (15), 2-methoxypropene (30), *trans*-cinnamaldehyde (4), *trans*-methylcinnamate (8), *trans*-crotonaldehyde (10), *trans*-methyl crotonate (10), dimethyl fumarate (7), dimethyl maleate (6), and maleic anhydride (5.5). The reaction temperatures, time, solvent used, composition of adducts, and isolated yields are given in Tables 1, 2, and 3. The reaction mixtures were evaporated to remove the solvent and excess of alkenes (if volatile) to give crude residues containing the cycloadducts which were then purified and analysed. 2-Methoxypropene did not give any characterizable products (sealed tube, toluene, 70 °C). Adducts containing the aldehyde group were not purified because of decomposition during purification.

Isomers of 2-*Hydroxymethylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**4c**) *and* (**5c**) *and its Conversion into the Methanesulphonates* (**4h**) *and* (**5h**).—The addition of (**1**) with allyl alcohol afforded a non-separable mixture of adducts (**4c**) and (**5c**) as an oil (84%); $\nu_{max.}$(neat) 3 367, 2 915, 2 840, 1 439, 1 256, 851, and 775 cm^{-1}; δ_H 1.04—3.12 (10 H, m), 3.16—4.44 (4 H, m), and 4.48 (1 H, s); *m/z* 157 (M^+ 5%). To a mixture of adducts (**4c**) and (**5c**) (514 mg, 3 mmol) in dry pyridine (3 ml) was added dropwise, methanesulphonyl chloride (570 mg, 5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After the removal of pyridine, a saturated solution of K_2CO_3 (15 ml) was added to the brown residue and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a light brown oily residue which was chromatographed over silica gel using 10% ether–dichloromethane as eluant to yield two fractions. The first component obtained was of the *adduct* (**5h**) as colourless needles (16%), m.p. 86—87 °C (ether–hexane) (Found: C, 46.15; H, 7.3; N, 5.9. $C_9H_{17}NO_4S$ requires C, 46.28; H, 7.28; N, 5.95%); $\nu_{max.}$(KBr) 2 923, 2 808, 1 358, 1 184, 1 005, 980, and 840 cm^{-1}; δ_H 1.08—2.60 (10 H, m), 3.10 (3 H, s), 3.40 (1 H, m), 4.10 (1 H, m), and 4.36 (2 H, m). The second component, *adduct* (**4h**), was isolated as an oil (79%) (Found: C, 46.9; H, 7.45; N, 6.1. $C_9H_{17}NO_4S$ requires C, 46.28; H, 7.28; N, 5.95%); $\nu_{max.}$(neat) 2 910, 2 833, 1 453, 1 350, 1 180, 980, and 830 cm^{-1}; δ_H 1.14—2.58 (10 H, m), 3.10 (3 H, s), 3.48 (1 H, m), and 4.30 (3 H, m); *m/z* 235 (M^+ 5.4%).

Isomers of Hexahydro-2H-*isoxazolo*[2,3-a]*pyridine*-2- *and* -3-*carbaldehyde* (**4g**)—(**7g**) *and their Conversion into the Methanesulphonates* (**4h**)—(**7h**).—The cycloaddition of (**1**) with acrylaldehyde afforded a mixture of four adducts, the ^1H n.m.r. spectrum of which displayed an aldehyde proton doublet at δ 9.85. The signal in the range δ 4.54—3.0 is too complex to be interpreted. The mixture of aldehydes was reduced with $NaBH_4$ to give a non-separable mixture of the alcohols (**4c**)—(**7c**) as an oil (96% yield in two steps), δ_H 1.04—2.06 (6 H, m), 2.38 (2 H, m), 2.63 (1 H, m), 3.06 (1 H, br), 3.40—3.98 (4 H, m), and 4.13 (1 H, t, *J* 8.0 Hz). The crude mixture of alcohols (**4c**)—(**7c**) (750 mg, 4.77 mmol) was methanesulphonated, using the procedure described for the preparation of compounds (**4h**) and (**5h**), to give a light brown oil which was an approximate 3:5:24:68 mixture of methanesulphonates (**4h**)—(**7h**) respectively. The composition of the methanesulphonates, hence the acrylaldehyde adducts, was determined by n.m.r. analysis of the methyl singlets around δ 3.0 of the crude methanesulphonates. This ratio was further supported by chromatographic separation of the methanesulphonates into two fractions. The first fraction contained a mixture of (**5h**) and (**7h**) as a white solid in 53% yield. The solid was recrystallized to give colourless needles of the *adduct* (**7h**), m.p. 56—57 °C (ether–hexane) (Found: C, 45.7; H, 7.3; N, 5.8. $C_9H_{17}NO_4S$ requires: C, 46.28; H, 7.28; N, 5.95%); $\nu_{max.}$(KBr) 2 940, 2 915, 1 362, 1 338, 1 178, 960, 852, and 838 cm^{-1}; δ_H 1.05—2.06 (6 H, m), 2.28 (1 H, m), 2.43 (1 H, m), 2.92 (1 H, m), 3.04 (3 H, s), 3.49 (1 H, m), 3.58 (1 H, dd, *J* 5.0 and 10.0 Hz), 4.17 (2 H, m), and 4.42 (1 H, dd, *J* 7.0 and 10.0 Hz); *m/z* 235 (M^+ 3%). The second fraction contained very little of the *adduct* (**4h**) and gave mainly the *adduct* (**6h**) as an oil (20%) (Found: C, 46.0; H, 7.45; N, 6.1. $C_9H_{17}NO_4S$ requires C, 46.28; H, 7.28; N, 5.95%); $\nu_{max.}$(neat) 2 920, 1 350, 1 175, 960, and 830 cm^{-1}; δ_H 1.12—2.24 (7 H, m), 2.49 (1 H, m), 2.68 (1 H, m), 3.06 (3 H, s), 3.48 (1 H, m), 3.67 (1 H, dd, *J* 5.5 and 8.0 Hz), 4.03 (1 H, t, *J* 8.0 Hz), and 4.30 (2 H, d, *J* 7.0 Hz).

Isomers of Hexahydro-2H-*isoxazolo*[2,3-a]*pyridine*-2- *and* -3-*carbonitrile* (**4f**)—(**7f**) *and their Conversion into the Methanesulphonates* (**4h**)—(**7h**).—The cycloaddition product from acrylonitrile contained a mixture of four adducts. The ^1H n.m.r. spectrum displayed complex signals in the range δ 3.4—5.0 and an i.r. (neat) peak at 2 240 cm^{-1}. Hydrogen chloride was bubbled through a solution of a mixture of the adducts (**4f**)—(**7f**) (0.540 g, 3.55 mmol) in anhydrous methanol (10 ml) at 0 °C until it was saturated. The reaction mixture was concentrated and made alkaline by addition of cold aqueous K_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 15 ml) and the organic extracts were dried ($MgSO_4$) and evaporated to afford the corresponding carboxymethyl derivatives (**4e**)—(**7e**), as a light brown oil (97%), $\nu_{max.}$(neat) 2 925, 1 735, 920, 857, and 742 cm^{-1}; the ^1H n.m.r. spectrum displayed two methyl singlets at δ 3.72 and 3.63 (4:1) and a complex pattern in the range δ 4.8—3.8. A solution of a mixture of the esters (**4e**)—(**7e**) (610 mg, 3.29 mmol) in anhydrous ether (5 ml) was added to a suspension of lithium aluminium hydride (0.2 g) in ether (25 ml) at −40 °C. The reaction mixture was warmed to 23 °C and stirred for 0.5 h. The mixture was then cooled and quenched by successive additions of water (0.2 ml), 10% aqueous sodium hydroxide (0.2 ml), and water (0.8 ml). The white solid was filtered off and washed with an excess of ether. The organic solution was dried ($MgSO_4$) and concentrated to give a pale yellow oil (87% yield) containing a mixture of the adducts (**4c**)—(**7c**), which was then methanesulphonated to give (**4h**)—(**7h**) by the procedure described earlier. The composition of the mixture of methanesulphonates, and hence the acrylonitrile adducts, was determined by chromatographic separation and ^1H n.m.r. analysis as before.

Isomers of 2- *and* 3-*Methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**4a**)—(**7a**) *from the Methanesulphonates* (**4h**)—(**7h**): *a General Procedure*.—A solution of Super-hydride in THF (6 ml, 6 mmol) was added to the methanesulphonate (**4h**) (471 mg, 2 mmol) at 23 °C and the mixture then stirred under nitrogen at 50 °C for 3 h. 10% Aqueous hydrochloric acid (10 ml) was then added to the cooled reaction mixture and the aqueous layer washed with ether (3 × 10 ml). After basification (K_2CO_3) the aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml). The CH_2Cl_2 solution was dried and concentrated under reduced pressure at 0 °C (the product is volatile) to give a faint yellow oil which was purified by passage through a short silica gel column using ether as eluant to give (**4a**) as an oil. In a similar manner (**5a**)—(**7a**) were prepared from (**5h**)—(**7h**) as oils. The isomers (**4a**) and (**5a**) were converted into (±)-sedridine and (±)-allosedridine respectively by reduction with lithium aluminium hydride in refluxing THF.[17]

Compound (**4a**) (79%) had $\nu_{max.}$(neat) 2 920, 1 450, 1 370, 1 265, 1 116, and 917 cm^{-1}; δ_H 1.04—2.60 (10 H, m), 1.26 (3 H, d, *J* 6.0 Hz), 3.46 (1 H m), and 4.22 (1 H, m).

Compound (**5a**) (70%) had $\nu_{max.}$(neat) 2 905, 2 830, 1 445, 1 370, 913, 862, and 745 cm^{-1}; δ_H 1.07—2.59 (10 H, m), 1.32 (3 H, d, *J* 6.5 Hz), 3.43 (1 H, m), and 4.23 (1 H, m).

Compound (**6a**) (73%) had $\nu_{max.}$(neat) 2 915, 2 850, 1 445, 1 350, 1 182, and 995 cm^{-1}; δ_H 1.02—2.60 (9 H, m), 1.09 (3 H, d, *J* 6.5 Hz), 3.46 (2 H, m), and 4.09 (1 H, t, *J* 8.0 Hz).

Compound (**7a**) (71%) had δ_H 1.01 (3 H, d, *J* 7.0 Hz), 1.10—1.94 (6 H, m), 2.16 (1 H, m), 2.43 (1 H, m), 2.58 (1 H, m), 3.40 (1 H, dd, *J* 5.0 and 8.0 Hz), 3.51 (1 H, m), and 4.19 (1 H, t, *J* 8.0 Hz).

Isomers of 2-*Acetoxymethyl*-2-*methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**12d**) *and* (**13d**).—The crude cycloaddition products were purified by chromatography with a 15% ether–dichloromethane mixture as eluant yielding two fractions. The first component isolated was *compound* (**12d**) as an oil (55%) (Found: C, 52.4; H, 8.0; N, 5.4. $C_{11}H_{19}NO_3$·HCl requires C, 52.90; H, 8.07; N, 5.61%); $\nu_{max.}$(neat) 2 925, 1 740, 1 443, 1 367, 1 303, 1 228, 1 030, 985, and 910 cm^{-1}; δ_H 1.06—2.56 (10 H, m), 1.28 (3 H, s), 2.09 (3 H, s), 3.41 (1 H, m), and 4.10 (2 H, br s); *m/z* 213 (M^+ 7.6%). The second component isolated was compound (**13d**) as an oil (11%), δ_H 1.14—2.60 (10 H, m), 1.38 (3 H, s), 2.11 (3 H, s), 3.42 (1 H, m), and 4.02 (2 H, AB, *J* 12.0 Hz).

Isomers of 2-*Dimethyl*-t-*butylsiloxymethyl*-2-*methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**12e**) *and* (**13e**).—The crude cycloaddition products were separated by chromatography using 7% ethyl acetate–dichloromethane as eluant. The first component, isolated as an oil, was assigned *structure* (**12e**) (40%) (Found: C, 62.3; H, 10.65; N, 4.8. $C_{15}H_{31}NO_2Si$ requires C, 63.10; H, 10.95; N, 4.91%); $\nu_{max.}$(neat) 2 915, 1 566, 1 245, 1 095, 1 052, 880, 832, and 768 cm^{-1}; δ_H 0.06 (6 H, s), 0.90 (9 H, s), 1.00—2.00 (8 H, m), 1.27 (3 H, s), 2.34 (2 H, m), 3.39 (1 H, m), 3.48 (1 H, d, *J* 9.5 Hz), and 3.63 (1 H, d, *J* 9.5 Hz); *m/z* 285 (M^+ 1.96%). The second component was obtained as an oil and was assigned structure (**13e**) (17%), $\nu_{max.}$(neat) 2 930, 1 475, 1 460, 1 440, 1 350, 1 250, 1 100, and 830 cm^{-1}; δ_H 0.05 (6 H, s), 0.89 (9 H, s), 1.00—2.00 (8 H, m), 1.31 (3 H, s), 2.40 (2 H, m), 3.40 (1 H, m), and 3.44 (2 H, AB, *J* 10.3 Hz); *m/z* 285 (M^+ 1.71%).

Isomers of 2-*Hydroxymethyl*-2-*methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**12c**) *and* (**13c**).—The crude cycloaddition products were isolated as white crystals from cold hexane (77% yield), the ^1H n.m.r. and i.r. spectra of which were virtually identical with those of (**12c**) derived from (**12a**) as described later. The crude adduct containing (**12c**) and (**13c**) were converted into a mixture of (**12d**) and (**13d**) by acetylation with Ac_2O and was silylated with dimethyl-t-butylsilyl chloride in imidazole in THF to give a mixture of (**12e**) and (**13e**). The major isomer was shown to be (**12c**).

Isomers of 2-*Methylhexahydro*-2H-*isozazolo*[2,3-a]*pyridin*-2-*ylmethyl Methanesulphonate* (**12i**) *and* (**13i**) *from* (**12c**) *and* (**13c**).—The crude mixture of adducts (**12c**) and (**13c**) was methanesulphonated as described for the preparation of (**4h**) to give a mixture of (**12i**) and (**13i**) which was separated, as oils, by chromatography with 15% ether–dichloromethane as eluant. Their relatively easy separation along with ^1H n.m.r. analysis in the range δ 4.0—4.5 of the methanesulphonate mixture allowed a better determination of adduct composition.

Compound (**12i**) (64% yield), $\nu_{max.}$(neat) 2 900, 1 440, 1 345, 1 260, 1 165, 1 110, 1 060, 970, and 885 cm^{-1}; δ_H 1.14—2.18 (8 H, m), 1.36 (3 H, s), 2.56 (2 H, m), 3.08 (3 H, s), 3.39 (1 H, m), 4.04 (1 H, d, *J* 10.5 Hz), and 4.42 (1 H, d, *J* 10.5 Hz); *m/z* 249 (M^+ 74%) and 99.

Compound (**13i**) (11%), $\nu_{max.}$(neat) 2 900, 1 450, 1 350, 1 260, 1 175, 1 120, 1 065, and 975 cm^{-1}; δ_H 1.10—2.54 (10 H, m), 1.38 (3 H s), 3.07 (3 H, s), 3.40 (1 H, m), and 4.11 (2 H, AB, *J* 10.5 Hz); *m/z* 249 (M^+ 73%) and 99.

2-*Methylhexahydro*-2H-*isozazolo*[2,3-a]*pyridine*-2-*carbaldehyde* (**12a**) *and its Conversion into* (**12i**) via (**12c**).—The crude cycloaddition product was an oil containing a single adduct (**12a**) (94%), $\nu_{max.}$(neat) 2 900, 2 805, 1 725, 1 450, 1 375, 1 263, 1 120, and 1 063 cm^{-1}; δ_H 1.02—2.66 (10 H, m), 1.32 (3 H, s), 3.50 (1 H, m), and 9.67 (1 H, s). The adduct (**12a**), on reduction with sodium borohydride in ethanol, yielded the *alcohol* (**12c**) as white crystals (87%), m.p. 55—56 °C (ether—hexane) (Found: C, 62.85; H, 9.8; N, 8.45. $C_9H_{17}NO_2$ requires C, 63.12; H, 10.01; N, 8.18%); $\nu_{max.}$(KBr) 3 300, 3 180, 2 940, 2 900, 1 460, 1 402, 1 380, 1 265, 1 145, 1 085, and 1 060 cm^{-1}; δ_H 1.10—2.24 (8 H, m), 1.24 (3 H, s), 2.38 (2 H, m), 3.43 (1 H, m), and 3.60 (2 H, AB, *J* 11.0 Hz, br OH underneath); *m/z* 171 (M^+ 39.4%). The crude alcohol (**12c**) was converted into (**12i**) by methanesulphonation as described earlier. T.l.c. or ^1H n.m.r. analysis failed to reveal the presence of the minor isomer (**13i**).

Isomers of Methyl 2-*Methylhexahydro*-2H-*isoxazolo*[2,3-a]-*pyridine*-2-*carboxylate* (**12b**) *and* (**13b**) *and their Conversion into* (**12i**) *and* (**13i**).—The mixture of adducts (**12b**) and (**13b**) was isolated as an oil (86%) (Found: C, 50.3; H, 7.6; N, 6.2. $C_{10}H_{17}NO_3$·HCl requires C, 50.95; H, 7.70; N, 5.94%); $\nu_{max.}$(neat) 2 918, 1 737, 1 443, 1 367, 1 293, 1 178, and 1 115 cm^{-1}; δ_H 1.09—2.89 (10 H, m), 1.50 (3 H, s), 3.53 (1 H, m), and 3.75 (3 H, s); *m/z* 199 (M^+ 5.8%). The mixture of adducts (**12b**) and (**13b**) was converted into the methanesulphonates (**12i**) and (**13i**) by reduction with lithium aluminium hydride followed by methanesulphonation as described earlier. The ^1H n.m.r. analysis determined the adduct ratio.

Isomers of 2-*Hydroxymethyl*-2-*methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridin*-2-*yltetrahydropyranyl Ether* (**12f**) *and* (**13f**) *and their Conversion into* (**12i**) *and* (**13i**).—A portion of the crude adducts was purified by chromatography with 20% ether–dichloromethane as eluant to give a mixture of (**12f**) and (**13f**) as an oil; $\nu_{max.}$(neat) 2 910, 1 438, 1 365, 1 255, 1 195, 1 110, 1 060, 1 030, and 983 cm^{-1}; δ_H 1.00—2.58 (16 H, m), 1.30, 1.32 (3 H, 2s), 3.10—4.10 (5 H, m), and 4.68 (1 H, m); *m/z* 255 (M^+ 13.7%). The adduct mixture was converted into (**12i**) and (**13i**) by hydrolysis with 5% hydrochloric acid solution, followed by methanesulphonation. As before, analysis of the ^1H n.m.r. spectrum of the mixture of the methanesulphonates (**12i**) and (**13i**) determined the ratio of (**12f**) and (**13f**).

Isomers of 2-*Methyl*-2-*phenylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**12g**) *and* (**13g**).—The mixture of crude adducts (**12g**) and (**13g**) was purified by chromatography with 4% ether–dichloromethane as eluant to yield two fractions. The first component (**12g**) was isolated as an oil (41%); $\nu_{max.}$(neat) 2 950, 1 493, 1 445, 1 373, 1 330, 1 285, and 1 065 cm^{-1}; δ_H 1.12—2.70 (10 H, m), 1.51 (3 H, s), 3.39 (1 H, m), and 7.14—7.54 (5 H, m). The second component (**13g**) was isolated as an oil (30%) (Found: C, 77.8; H, 8.45; N, 6.5. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45%); $\nu_{max.}$(neat) 2 920, 1 495, 1 448, 1 045, and 883 cm^{-1}; δ_H 1.08—2.52 (9 H, m), 1.68 (3 H, s), 2.63 (1 H, m), 3.54 (1 H, m), and 7.18—7.58 (5 H, m).

2-*Phenylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-3-*carbaldehyde* (**16a**) *and its Reduction to* (**16f**).—The crude cycloaddition product was obtained as a yellow oil, gradually darkening to a light brown: $\nu_{max.}$(neat) 2 910, 2 805, 1 715, and 1 448 cm^{-1}; δ_H 1.12—2.18 (6 H, m), 2.79 (1 H, m), 3.09 (1 H, m), 3.60 (1 H, m), 5.43 (1 H, d, *J* 4.5 Hz), 7.39 (5 H, m), and 9.97 (1 H, d, *J* 3.3 Hz). The crude adduct was reduced with sodium boro-

hydride in ethanol to give 3-*hydroxymethyl*-2-*phenylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**16f**) as white crystals (95%), m.p. 86—87 °C (ether–hexane) (Found: C, 72.6; H, 8.5; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.01%); $\nu_{max.}$(KBr) 3 180, 2 918, 2 858, 1 453, 1 398, 1 050, and 995 cm^{-1}; δ_H 1.20—2.12 (6 H, m), 2.40—2.76 (3 H, m), 3.12 (1 H, br), 3.58 (1 H, m), 3.90 (2 H, ABX, *J* 4.3 and 11.0 Hz), 5.08 (1 H, d, *J* 3.5 Hz), and 7.42 (5 H, m).

Isomers of Methyl 2-*Phenylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-3-*carboxylate* (**16b**) *and* (**17b**) *and their Conversion into* (**16f**) *and* (**17f**).—The ^{1}H n.m.r. spectrum of the crude adducts revealed the presence of (**16b**) and (**17b**) in an 87:13 ratio as determined by the integration of their C-2 protons at δ 5.45 and 5.32. The adducts were purified by chromatography with 5% ethyl acetate–dichloromethane as eluant to yield two fractions. The first component, isolated as an oil, was the minor isomer (**17b**) (10%); $\nu_{max.}$(neat) 2 920, 1 735, 1 435, 1 348, 1 262, 1 190, 1 163, and 997 cm^{-1}; δ_H 1.10—2.00 (6 H, m), 2.60 (2 H, m), 3.18 (1 H, dd, *J* 6.3 and 10.5 Hz), 3.58 (1 H, m), 3.80 (3 H, s), 5.32 (1 H, d, *J* 6.3 Hz), and 7.46 (5 H, m); *m/z* 261 (M^+ 22%), 162 and 99. The second component, the major *isomer*, was isolated as colourless needles, and assigned structure (**16b**) (69%), m.p. 53—54 °C (ether–hexane) (Found: C, 68.8; H, 7.2; N, 5.4. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%); $\nu_{max.}$(KBr) 2 900, 2 830, 1 730, 1 458, 1 440, 1 400, 1 300, 1 290, 1 266, 1 216, 1 178, and 1 016 cm^{-1}; δ_H 1.20—2.20 (6 H, m), 2.66 (2 H, m), 3.26 (1 H, dd, *J* 5.5 and 8.5 Hz), 3.62 (1 H, m), 3.76 (3 H, s), 5.45 (1 H, d, *J* 5.5 Hz), and 7.40 (5 H, m). A portion of the original mixture of crude adducts (**16b**) and (**17b**) was reduced with lithium aluminium hydride to give (**16f**) and (**17f**) in a ratio of 87 : 13 as determined by ^{1}H n.m.r. integration at δ 5.08 (d, *J* 3.5 Hz for major isomer) and 4.78 (d, *J* 5.5 Hz for minor isomer).

2-*Methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-3-*carbaldehyde* (**16c**) *and its Conversion into the Methanesulphonate* (**16h**).—The crude cycloaddition product revealed the presence of the single adduct (**16c**) as a light yellow oil; $\nu_{max.}$(neat) 2 845, 2 725, 1 715, 1 445, 1 385, 1 228, 1 118, and 1 030 cm^{-1}; δ_H 1.00—2.06 (6 H, m), 1.34 (3 H, d, *J* 6.2 Hz), 2.52 (2 H, m), 2.70 (1 H, m), 3.51 (6 H, m), 4.50 (1 H, dq, *J* 4.5 and 6.2 Hz), and 9.87 (1 H, d, *J* 4.2 Hz). The adduct (**16c**) was reduced with sodium borohydride to afford (**16g**) as an oil (86%), $\nu_{max.}$(neat) 3 385, 2 910, 1 438, 1 375, 1 320, 1 103, 1 038, and 730 cm^{-1}; δ_H 1.08—2.00 (6 H, m), 1.31 (3 H, d, *J* 6.5 Hz), 2.11 (1 H, m), 2.39 (2 H, m), 3.10 (1 H, br), 3.44 (1 H, m), 3.75 (2 H, ABX, *J* 5.0 and 10.5 Hz), and 4.15 (1 H, dq, *J* 3.8 and 6.5 Hz). The alcohol (**16g**) was methanesulphonated in the usual way to give the methanesulphonate (**16h**) as colourless plates (81%), m.p. 83—84 °C (ether) (Found: C, 48.1; H, 7.7; N, 6.0. $C_{10}H_{19}NO_4S$ requires C, 48.17; H, 7.68; N, 5.62%); $\nu_{max.}$(KBr) 2 915, 1 398, 1 355, 1 340, 1 178, and 1 010 cm^{-1}; δ_H 1.08—2.08 (7 H, m), 1.35 (3 H, d, *J* 6.0 Hz), 2.42 (2 H, m), 3.03 (3 H, s), 3.46 (1 H, m), 3.87 (1 H, dq, *J* 4.0 and 6.0 Hz), 4.21 (1 H, dd, *J* 8.5 and 9.5 Hz), and 4.42 (1 H, dd, *J* 6.5 and 9.5 Hz).

Isomers of Methyl 2-*Methylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-3-*carboxylate* (**16d**) *and* (**17d**) *and their Conversion into the Methanesulphonates* (**16h**) *and* (**17h**).—The crude products were purified by passage through a short silica gel column using ether as eluant to give a non-separable mixture of the *adducts* (**16d**) and (**17d**) (90:10) as an oil (94%) (Found: C, 50.55; H, 7.9; N, 6.2. $C_{10}H_{17}NO_3$·HCl requires C, 50.95; H, 7.70; N, 5.94%); $\nu_{max.}$(neat) 2 910, 2 830, 1 730, 1 430, 1 375, 1 330, 1 280, 1 260, 1 175, 1 110, 1 045, and 1 060 cm^{-1}; δ_H 1.12—2.16 (6 H, m), 1.34 (3 H, d, *J* 6.0 Hz), 2.46 (2 H, m), 2.88 (1 H, dd, *J* 6.0 and 8.0 Hz), 3.54 (1 H, m), 3.75 (3 H, s), and 4.53 (1 H, quint., *J* 6.0 Hz). A minor quintet appeared at δ_H 4.36 (*J* 6.5 Hz) due to the 2-H of the minor isomer (**17d**). Integration of the C-2 protons gave the adduct ratio. The mixture of adducts (**16d**) and (**17d**) was reduced with lithium aluminium hydride to give (**16g**) and (**17g**) (83% yield). The methanesulphonation of this mixture of alcohols gave a non-separable mixture of the methanesulphonates (**16h**) and (**17h**) (85% yield). The ^{1}H n.m.r. spectrum displayed SO_2Me singlets at δ 3.03 (major) and 3.05 (minor).

Isomers of trans-*Dimethyl Hexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-2,3-*dicarboxylate* (**16e**) *and* (**17e**).—The adduct ratio was determined by integration of the C-2 protons. The mixture of adducts (**16e**) and (**17e**) was purified by chromatography with 3% ethyl acetate–dichloromethane as eluant to yield two fractions. The first component, the minor isomer, was isolated as an oil, and assigned structure (**17e**) (36%), $\nu_{max.}$(neat) 2 930, 2 840, 1 730, 1 425, 1 275, 1 200, 1 110, and 1 005 cm^{-1}; δ_H 1.00—2.24 (6 H, m), 2.52 (2 H, m), 3.42 (1 H, dd, *J* 5.5 and 10.0 Hz), 3.56 (1 H, m), 3.78 (3 H, s), 3.80 (3 H, s), and 4.84 (1 H, d, *J* 5.5 Hz); *m/z* 243 (M^+ 14.4%) and 99. The second component, the major *isomer* (**16e**), was isolated as white crystals (53%), m.p. 65—66 °C (ether) (Found: C, 53.7; H, 7.0; N, 5.95. $C_{11}H_{17}NO_5$ requires C, 54.31; H, 7.04; N, 5.76%); $\nu_{max.}$(KBr) 2 935, 2 890, 1 734, 1 445, 1 398, 1 276, 1 262, 1 225, and 1 178 cm^{-1}; δ_H 1.08—2.04 (6 H, m), 2.54 (2 H, m), 3.48 (1 H, dd, *J* 5.0 and 8.0 Hz), 3.58 (1 H, m), 3.78 (3 H, s), 3.80 (3 H, s), and 5.03 (1 H, d, *J* 5.0 Hz); *m/z* 243 (M^+ 2.8%).

Isomers of cis-*Dimethyl Hexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-2,3-*dicarboxylate* (**18a**) *and* (**19a**).—The non-separable mixture of adducts (**18a**) and (**19a**) was purified by silica gel chromatography to give an oil (93% yield) (Found: C, 54.0; H, 7.2; N, 5.9. $C_{11}H_{17}NO_5$ requires C, 54.31; H, 7.04; N, 5.76%); $\nu_{max.}$(neat) 2 925, 2 835, 1 740, 1 435, 1 340, and 1 050 cm^{-1}; δ_H 1.15—2.23 (6 H, complex), 2.69 (2 H, m), 3.41 (1 H, t, *J* 10.0 Hz), 3.55 (1 H, m), 3.68 (3 H, s), 3.73 (3 H, s), and 4.74 (1 H, d, *J* 10.0 Hz). N.m.r. peaks for the minor isomer could not be detected readily. All peaks were overlapping except for a minor doublet (*J* 9.0 Hz) which appeared at δ 5.03 due to the 2-H of (**19a**).

Reaction of the Nitrone (**1**) *with Maleic Anhydride*.—The ^{1}H n.m.r. spectrum of the crude cycloaddition product (98% yield) revealed the presence of two isomers (**18b**) and (**19b**). The isomer ratio was determined by the conversion of the adducts into the corresponding diols as described previously. An analytical sample was prepared by crystallizing a portion of the crude product from dichloromethane, m.p. 139—140 °C (decomp.) (Found: C, 54.45; H, 5.45; N, 7.3. $C_9H_{11}NO_4$ requires C, 54.81; H, 5.62; N, 7.10%); $\nu_{max.}$(KBr) 3 095, 2 945, 1 775, 1 452, 1 402, 1 275, and 1 056 cm^{-1}; δ_H 1.15—1.95 (6 H, m), 3.04 (1 H, m, NCH_2), 3.45 (1 H, d, *J* 7.8 Hz, 3-H), 3.59 (1 H, m, NCH_2), 3.75 (1 H, t, *J* 7.0 Hz, 4-H), and 5.01 (1 H, d, *J* 7.8 Hz, 2-H).

Isomers of 2,3-*Dihydroxymethylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**16j**) *and* (**17j**), (**18c**) *and* (**19c**).—Lithium aluminium hydride reduction of (**16e**) in ether afforded the *adduct* (**16j**) as an oil (89%), $\nu_{max.}$(neat) 3 300, 2 895, 2 820, 1 938, 1 050, and 878 cm^{-1}; δ_H 1.00—2.59 (9 H, m), 2.61—3.44 (2 H, br), 3.48 (1 H, m), 3.67 (4 H, m), and 4.16 (1 H, q, *J* 4.0 Hz). Similar reaction of (**17e**) gave the *adduct* (**17**j) as white crystals (84%), m.p. 95—96 °C (ether–dichloromethane) (Found: C, 57.9; H, 9.3; N, 7.7. $C_9H_{17}NO_3$ requires C, 57.73; H, 9.15; N, 7.48%; $\nu_{max.}$(KBr) 3 328, 3 108, 2 910, 1 443, 1 403, 1 381, 1 110, and 1 042 cm^{-1}; δ_H 1.08—2.22 (7 H, m), 2.42 (2 H, m), 2.60—3.34 (2 H, br), 3.45 (1 H, m), 3.76 (4 H, m), and 3.95 (1 H, q, *J* 5.0 Hz). Reduction of the mixture of adducts (**18a**) and (**19a**) in ether (88% yield) and the reduction of (**18b**) and (**19b**) in THF resulted in the formation of a similar mixture of non-separable diols (**18c**) and (**19c**) as white crystals (61%), m.p. 86—87 °C (ether–dichloromethane); $\nu_{max.}$(KBr) 3 080, 2 850, 1 480, 1 452, 1 438, 1 400, 1 265, 1 060,

and 1 040 cm^{-1}; δ_H 1.08—2.96 (9 H, m), 3.48 (1 H, m), 3.86 (6 H, m), and 4.26, 4.50 (1 H, m).

*Isomers of Hexahydro-2*H*-isoxazolo*[2,3-a]*pyridine* 2,3-*diyldimethyl Bismethanesulphonate* (**16k**), (**17k**), (**18d**), *and* (**19d**).—As described before, the diols (**16j**) and (**17j**) and the mixture of (**18c**) and (**19c**) were methanesulphonated to give compounds (**16k**), (**17k**), (**18d**), and (**19d**) respectively.

Compound (**16j**), white crystals (72%), m.p. 119—120 °C (ether) (Found: C, 38.2; H, 6.1; N, 3.9. $C_{11}H_{21}NO_7S_2$ requires C, 38.47; H, 6.16; N, 4.08%); $\nu_{max.}$(KBr) 2 920, 1 340, 1 175, 1 000, and 962 cm^{-1}; δ_H 1.08—2.00 (7 H, m), 2.42 (1 H, m), 2.72 (1 H, m), 3.06 (3 H, s), 3.08 (3 H, s), 3.48 (1 H, m), 4.09 (1 H, q, *J* 4.5 Hz), and 4.20—4.52 (4 H, m).

Compound (**17j**), an oil (85%); δ_H 1.12—2.24 (7 H, m), 2.52 (1 H, m), 2.67 (1 H, m), 3.11 (6 H, s), 3.52 (1 H, m), and 4.76—4.14 (5 H, m).

The mixture of methanesulphonates (**18d**) and (**19d**), obtained from the maleic anhydride adducts (**18b**) and (**19b**), was purified by chromatography with 10% ethyl acetate to yield two fractions. The component isolated as colourless needles was assigned structure (**19d**) (6%), m.p. 123—124 °C (Found: C, 38.4; H, 5.95; N, 4.3. $C_{11}H_{21}NO_7S_2$ requires C, 38.47; H, 6.16; N, 4.08%); $\nu_{max.}$(KBr) 2 932, 2 910, 1 348, 1 182, 962, and 840 cm^{-1}; δ_H 1.05—2.05 (7 H, m), 2.53 (2 H, m), 3.07 (3 H, s), 3.11 (3 H, s), 3.45 (1 H, m), 4.31 (1 H, m), and 4.46 (4 H, m). The second component, the major isomer (**18d**), was isolated as white crystals (49%), m.p. 79—80 °C (ether) (Found: C, 38.8; H, 6.0; N, 3.9. $C_{11}H_{21}NO_7S_2$ requires C, 38.47; H, 6.16; N, 4.08%); $\nu_{max.}$(KBr) 2 940, 2 915, 1 355, 1 175, 975, 838, and 753 cm^{-1}; δ_H 1.12–2.24 (7 H, m), 2.50 (1 H, m), 2.79 (1 H, m), 3.07 (3 H, s), 3.07 (3 H, s), 3.49 (1 H, m), and 4.42 (5 H, m). The mixture of methanesulphonates (**18d**) and (**19d**), obtained from the dimethyl maleate adducts (**18a**) and (**19a**), contained a similar ratio of major and minor isomers as above.

Isomers of cis- *and* trans-2,3-*Dimethylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**16i**), (**17i**), *and* (**18e**) *from the Reaction of Super-hydride with the Methanesulphonates* (**16h**), (**16k**), (**17k**), *and* (**18d**).—The reactions were carried out using the same procedure described earlier under the general procedure for Super-hydride reaction, except that the temperature was maintained at 65 °C. The yields of these reactions varied in the range 65—75%. The compounds (**16h**) and (**16k**) gave (**16i**) as an oil, δ_H 0.99 (3 H, d, *J* 7.0 Hz), 1.10—2.16 (7 H, m), 1.29 (3 H, d, *J* 6.0 Hz), 2.28 (1 H, m), 2.45 (1 H, m), 3.48 (1 H, m), and 3.67 (1 H, quintet, *J* 6.0 Hz). The methanesulphonate (**17k**) afforded (**17i**) as an oil, δ_H 1.04 (3 H, d, *J* 6.5 Hz), 1.08—2.00 (7 H, m), 1.31 (3 H, d, *J* 6.5 Hz), 2.43 (2 H, m), 3.43 (1 H, m), and 3.72 (1 H, quintet, *J* 6.5 Hz). The methanesulphonate (**18d**) afforded (**18e**) as an oil, δ_H 0.95 (3 H, d, *J* 7.0 Hz), 1.00—2.00 (7 H, m), 1.13 (3 H, d, *J* 6.5 Hz), 2.43 (2 H, m), 3.44 (1 H, m), and 4.26 (1 H, dq, *J* 6.5 and 9.0 Hz).

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