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Nitrone Cycloaddition : Peracid Oxidation of Perhydro-1,2-oxazolo[3,2-c][1,4]oxazines

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***Abstract** : Regiochemistry of peracid induced ring opening of perhydro-1,2-oxazolo[3,2-c][1,4]oxazines (2) and (6) in aprotic solvent is dictated by orientation of lone pair of electrons on nitrogen. In contrast to the case with the corresponding hexahydro-2H-isoxazolo[2,3-a]pyridines (17), the oxidation of (2) gives mainly an equilibrium mixture of aldonitrone (3) and its hydroxylamine tautomer (4) which undergo stereoselective cycloaddition with styrene and methyl methacrylate. The X-ray diffraction study reveals the 6-5 ring system in (2) to be cis fused.*

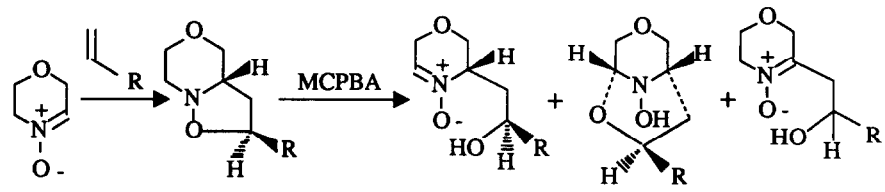
INTRODUCTION

Among the plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemists.[1] The nitrone cycloadditon reactions, being the best chemical template for constructing isoxazolidines, have found widespread use in the synthesis of natural products.[1] Nitrones generated by oxidation of isoxazolidines with peracids marked the beginning of the utilization of the second-generation nitrones, which have been successfully employed in the synthesis of a number of alkaloids.[2]

Even though the peracid induced ring opening of the isoxazolidines has been known for three decades,[3] a clearer picture of the mechanistic pathway this reaction traverses is emerging through our continuing efforts.[4] In order to establish firmly the mechanism, herein, we report the correlation between the regiochemistry of the ring opening reactions of the perhydro-1,2-oxazolo[3,2-c][1,4]oxazines (**2**) and their conformational properties. We also report for the first time the conformation of the 6/5 fused ring system in (**2**) in the solid state as determined by the X-ray diffraction study.

RESULTS AND DISCUSSION

Regiochemical details of the peracid oxidation along with reaction temperature and solvent are given in Table 1. In contrast to earlier findings,[4] m-chloroperbenzoic acid oxidation of the nitrone (**1**)-styrene adduct (**2a**) in dichloromethane afforded a mixture of three products; - in addition to aldo- (**3a**)



(1) (2) (3) (4) (5)

a, R = Ph; **b**, R = CH_2OH

Scheme 1

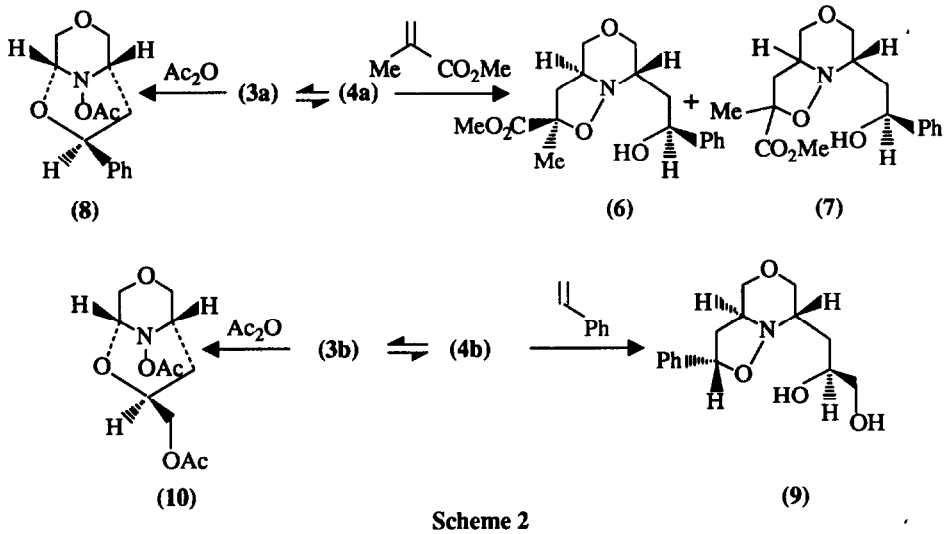
Table 1. Regiochemistry of MCPBA Oxidation of Isoxazolidines (2)

Isoxazolidine	Solvent	Temp/°C	Composition of Products (3)+(4)	(5)
2a	CH_2Cl_2	-10	80	20
	CH_3OH	0	35	65
	HOAc	20	35	65
2b	CH_2Cl_2	-10	90	10
	HOAc	20	35	65

and keto-nitrone (**5a**), a bicyclic hydroxylamine (**4a**), tautomeric to the aldonitrone (**3a**), was also obtained (Scheme 1). The ^1H NMR spectrum of the crude products displayed signals at δ 5.10 (dd, J 4.0, 8.0 Hz), 5.85 (dd, J 4.0, 12.0 Hz) and 5.18 (dd, J 3.5, 7.5 Hz) assigned to the benzylic protons of (**3a**), (**4a**), and (**5a**), respectively. Although there is a big difference among the R_f values of the hydroxylamine (**4a**) and the more polar nitrones (**3a**) and (**5a**), we were unable to isolate (**4a**) by chromatography since it quickly tautomerized to give a mixture of (**3a**) and (**4a**). Chromatographic separation afforded the ketonitrone (**5a**), and it does not tautomerize to give the strained four-membered ring system. The ratio of (**3a**), (**4a**), and (**5a**) was determined by integration of benzylic proton signals and found to be 15 : 65 : 20, respectively. Likewise, nitrone (**1**)-allyl alcohol adduct (**2b**), on peracid oxidation in CH_2Cl_2 gave a mixture of (**3b**)+(**4b**) and (**5b**) in a ratio of 90 : 10, respectively (See Experimental). Switching the solvent from dichloromethane to methanol or acetic acid led to a reversal in the regioselection of the peracid reaction affording a mixture of (**3a**)+(**4a**) and (**5a**) in a respective ratio of 35 : 65 in each case.

Although we were unable to obtain (**3a**) and (**4a**) in their pure forms, a mixture of (**3a**), (**4a**) and (**5a**) underwent a second sequence of addition reaction with methyl methacrylate at 20°C to give (**6**) as the predominant adduct, with minor quantity of isomeric product (**7**) with unassigned stereochemistry (Scheme 2). The ketonitrone (**5a**) remained unreacted under the reaction conditions. The tautomeric hydroxylamine (**4a**) was not present at the end, thus establishing its equilibration to the nitrone (**3a**) which in turn was trapped by methyl methacrylate. The stereochemistry of the adduct (**6**) was based on

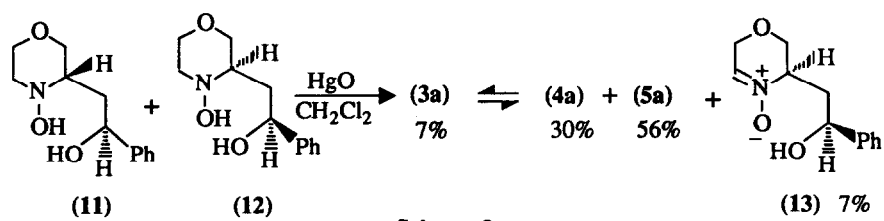
preceding works[2,4b,5] which demonstrated the marked tendency of the alkene to approach from the less hindered face of the nitrone and preference of methoxycarbonyl group to be *endo* oriented due to favourable secondary orbital interactions in the transition state.[6] Treatment with acetic anhydride locks the equilibration mixture into the non-equilibrating mono-acetate (**8**) as a crystalline compound, thus confirming the presence of the bicyclic derivative. Spectral analysis readily identified the product. IR spectrum revealed the presence of the ester functionality at 1762 cm^{-1}. Similar to the N-hydroxy compound (**4a**), the benzylic proton of (**8**) appeared at unusually downfield (δ 5.88, dd, J 4.5, 12.0 Hz). The mixture of compounds (**3b**), (**4b**) and (**5b**), likewise, underwent addition reaction with styrene to give the adduct (**9**) stereospecifically along with minor quantity of the unreacted nitrone (**5b**). The



Scheme 2

presence of the bicyclic hydroxylamine (**4b**) was confirmed by its reaction with acetic anhydride to give the diacetate (**10**).

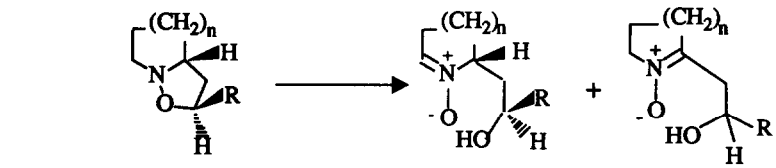
Since the peracid oxidation reaction involves aqueous work up which may promote the tautomerization process, we decided to prepare the nitrones under aprotic conditions. Thus, a mixture of hydroxylamines (**11**) and (**12**), obtained by sodium borohydride reduction of a mixture of (**3a**), (**4a**) and (**5a**), upon mercury(II) oxide oxidation in dichloromethane afforded a mixture of nitrones (**3a**), (**5a**), and (**13**) as expected (Scheme 3). The ^1H NMR spectrum did not reveal the presence of the tautomer (**4a**).



Scheme 3

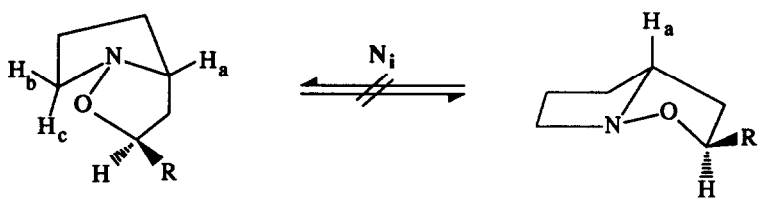
However, the ^1H NMR spectrum taken after 2 h and 48 h at 20°C revealed the presence of the tautomer **(4a)** to the extent of 5% and 30%, respectively, of the total products. The proportion of the tautomer did not change further with time. The equilibrium ratio of **(3a)**, **(4a)**, **(5a)** and **(13)** was found to be 7 : 30 : 56 : 7, respectively.

For an interpretation of the regiochemical behaviour observed in the peracid induced ring opening of the isoxazolidines **(2)** and its counterparts **(14)**, and **(17)** (Scheme 4), one has to take a closer look at the orientation of the lone pair of electrons on nitrogen.[4] While the cycloadducts **(14)**, on peracid treatment in dichloromethane lead to regiospecific formation of the aldonitrones **(15)**, lack of regioselectivity in the oxidation of the isoxazolidines **(17)**, leading mainly to the ketonitrones **(19)**, severely hampers its synthetic application.[3a,4] Geometric constraints do not permit nitrogen inversion (N_i) in the isoxazolidine **(14)**, which must remain *cis* fused.[4,8] However, the 6-5 fused systems, as exemplified by isoxazolidines **(2)** and **(17)**, can in principle, exist in three different conformations. While the *cis* pair **A** and **B** is in rapid equilibrium by chair inversion (C_i), one of the *cis* conformers **B** is converted into the *trans* conformer by a relatively slow nitrogen inversion process (N_i).[4,8] Recent NMR

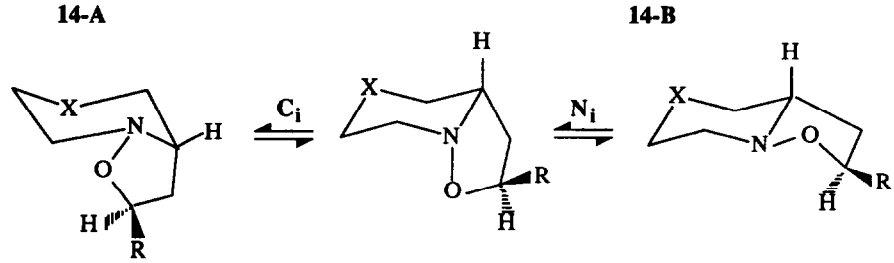


n = 1 **(14)** **(15)** **(16)** **a**, R = Ph

n = 2 **(17)** **(18)** **(19)** **b**, R = CH_2OH



14-A **14-B**



X = CH_2 **17-A** **17-B** **17-C** (major)

X = O **2-A** **2-B** **2-C** (minor)

Scheme 4

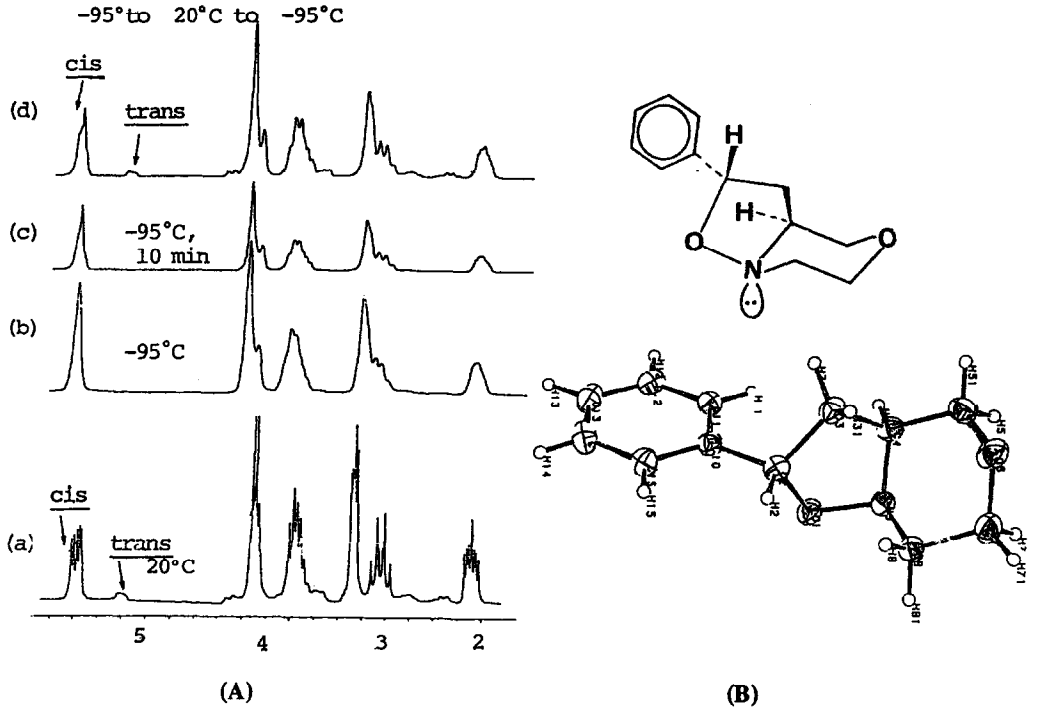


Figure 1. (A) (a) Represents ^1H spectrum at 20°C, (b) ^1H spectrum at -95°C, (c) ^1H spectrum at -95°C after 10 min, (d) ^1H spectrum after warming to 20°C and then cooling to -95°C.
(B) ORTEP representation of the isoxazolidine (**2a**).

studies[8] involving a series of cycloadducts (**2**) and (**17**) have shown the major isomer to be the *trans* conformer C for the isoxazolidines (**17**) and the *cis* pair **B** and C for (**2**). Indeed X-ray diffraction study of one such cycloadduct having the ring system of (**17**) has shown to have the *trans* conformation in the solid state.[9] To confirm the NMR findings for the other system, the adduct (**2a**) was subjected to X-ray crystallographic analysis. The result of the study is shown in Figure 1 and is in agreement with the NMR assignments of *cis* fusion to the major conformer of (**2a**); and in the crystalline state[10] it adopts the conformation **2-A** with oxygen substituent being in the equatorial environment. Needless to say, the favourable conformation in the solid state, as dictated by the crystal packing forces, may not be the conformation of choice in the solution. However, it was found that the isoxazolidine (**2a**) prefers to be in

the *cis* conformation in the solid as well as in the solution. Thus, a few crystals of (**2a**) were added to cooled (-150°C) CD_2Cl_2 in an NMR tube and the proton spectrum, recorded at -95°C, revealed the presence of only one isomer, a broad quartet at δ 5.46 corresponding to the major *cis* isomer, with no peaks at δ 5.04 for the minor isomer. After 10 minutes, the sample was warmed to room temperature and then the spectrum recorded at -95°C revealed the presence of both *cis* and *trans* conformers. Geometry of the ring fusion would indeed provide vital information in explaining the regiochemistry of the peracid induced ring opening of the isoxazolidines. Composition of the conformers and regiochemistry of peracid induced ring opening of the isoxazolidines (**2**), (**14**) and (**17**) are included in Table 2. While the population ratios were measured in $CDCl_3$ at 25°C, the peracid reactions were carried out in CH_2Cl_2 at -10°C. Population ratios are, to some extent, dependent on temperature and solvent. However, it is evident from the table that the population ratio of the isoxazolidines and the ratio of the regiomeric

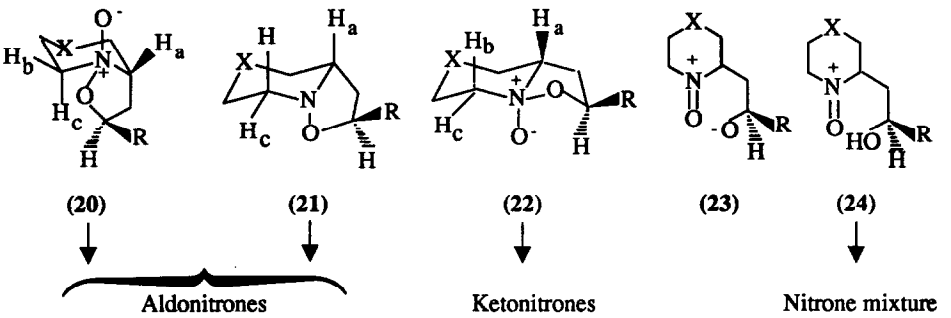
Table 2. Composition of Conformers and Regiochemistry of MCPBA Induced Ring Opening of the Isoxazolidines.

Cycloadduct		%Composition of Conformers[a]		%Composition of the Nitrones[b]	
		cis pair	*trans*	aldonitrones	ketonitrones
				(3)	(4)
14	**a**, R = Ph	100	0	100	0
	b, R = CH_2OH	100	0	100	0
				(7)	(8)
17	**a**, R = Ph	22	78	35	65
	b, R = CH_2OH	42	58	30	70
				(11+12)	(13)
2	**a**, R = Ph	80	20	80	20
	b, R = CH_2OH	100	0	~90	10

[a]in $CDCl_3$ at 25°C; [b]peracid reaction ran in CH_2Cl_2 at -10°C.

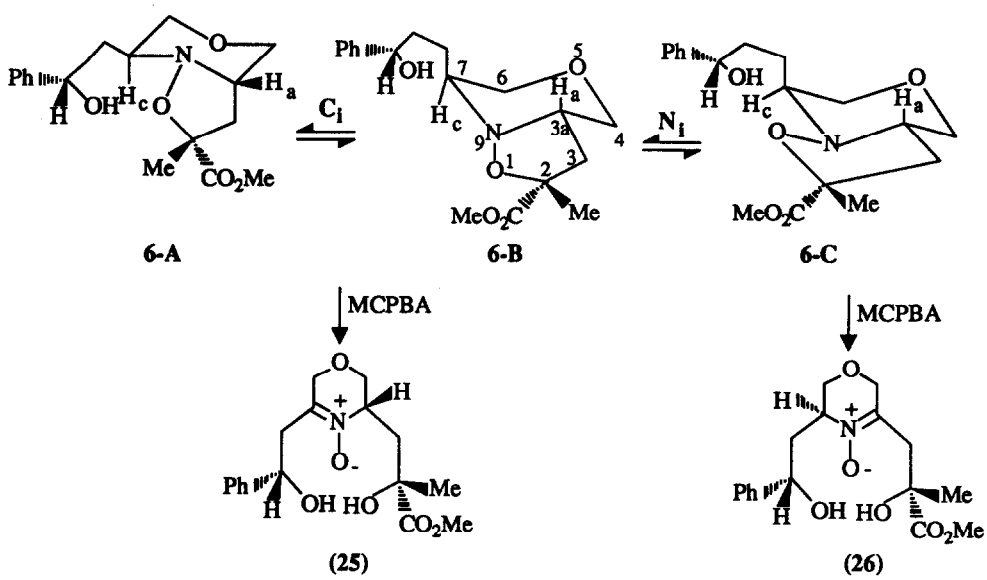
nitrones are quite similar. The mechanistic pathway envisages the intermediacy of the amine oxide intermediate (**20**), (**21**), and (**22**) followed by formation of nitroxonium salts (**23**) in which the alkoxide ion helps fast kinetic deprotonation to result in the formation of the nitrones (Scheme 5). Electrostatic attraction, presumably, holds the ion pair in the salts close to each other and restricts rotation long enough to allow the selective deprotonation to occur. While the alkoxide ion in **23**, obtained from the *cis* pair of amine oxides **20** and **21**, finds H_c in its immediate vicinity for deprotonation to give the aldonitrones, the

salt derived from the *trans* amine oxide **22**, affords the ketonitrones by abstraction of the proton H_a. In a protic solvent such as methanol or acetic acid, involvement of the protonated species (**24**) changes the mechanistic course and the composition of the product nitrones reflects the relative stability of the aldo- and keto-nitrones. A simple rule is emerging through our continuing works : in the peracid induced ring opening reaction, the *cis* conformers lead to aldonitrone and the *trans* conformer gives the ketonitrone regiomer. However, implementation of the rule requires that the barrier to nitrogen inversion must be of higher or comparable magnitude to that of the activation barrier for the peracid oxidation. In such cases, the Curtin-Hammet principle[11] may not apply. As such, the ratio of product would very much depend on the population ratio of the starting conformers. While the barrier to nitrogen inversion in isoxazolidines (**2**) and (**17**) has been found to be very high (~68 kJ/mole)[8], the activation barrier for peracid oxidation, which happens very fast at -10°C, are yet to be known.



Scheme 5

For a further understanding of the peracid reaction, we decided to investigate the oxidation of the second-cycloadduct (**6**) which again may exist in three different conformations as shown in Scheme 6. In contrast to cycloadducts (**2**) and (**17**), the ^1H NMR signals for the compound (**6**) were very sharp indicating the presence of either the *cis* pair **6-A** and **6-B** or the *trans* fused isomer **6-C**. Since the isoxazolidine (**2**) favours the *cis* fusion, it is quite logical to assume the same ring fusion for the adduct (**6**). The *trans* conformer **6-C** has the added disadvantage of having an axial substituent at C-7. Of the *cis* pair, **6-A** should be the predominant conformer since it has only one axial substituent at C-3a. To be in line with the mechanistic pathway, the peracid oxidation of (**6**) in aprotic solvent should give the nitrone (**25**) as the sole regiomer since the alkoxide ion in the nitroxonium salt(s), derived from the *cis* pair **6-A** and **6-B**, would find H_c in its immediate vicinity for kinetic deprotonation. To our delight, the peracid oxidation in dichloromethane resulted in the exclusive formation of the nitrone (**25**) in quantitative yield. The oxidation in protic solvent methanol afforded, as expected, a mixture of the nitrones (**25**) and (**26**) in a respective ratio of 65 : 35. The ^1H NMR spectra readily identified the nitrones (**25**) and (**26**); benzylic proton of the former, being closer to the nitrone functionality, appears at downfield (δ 5.21) compared to the benzylic proton of the latter (δ 5.04).



CH_2Cl_2	100	:	0
MeOH	65	:	35

Scheme 6

The mechanism of the peracid reaction is now firmly established through our study which would indeed provide valuable guidelines regarding the preparation of second-generation nitrones from nitrone-alkene addition products. The work also represents how a subtle difference in the ring skeleton changes the conformational preference for the isoxazolidines (**2**) and (**17**).

EXPERIMENTAL

All m.p.s are uncorrected. Elemental analysis were performed on a Carlo-Erba 1106 Elemental Analyzer. IR spectra were recorded on a Nicolet 5 DBX FT IR spectrometer and are reported in wave numbers (cm^{-1}). 70 eV E. I. mass spectra were recorded on a JEOL JMS-HX 100 system. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). HPLC grade dichloromethane was dried ($MgSO_4$) and passed through activated alumina. The cycloadducts (**2a**) and (**2b**) were prepared as described.[12] ^1H NMR spectra were recorded on a Brucker AC 80 using deuteriated chloroform with Me_4Si as internal standard.

MCPBA Oxidation of the Adduct (2a) and Reaction of the Ring Opened Products with Methyl Methacrylate.-

(i) in dichloromethane : To a solution of the adduct (**2a**) (403 mg, 1.97 mmol) in CH_2Cl_2 (30 cm^3) at -10°C was added MCPBA (90% purity, 2.17 mmol). The reaction mixture was stirred at -10°C for 1 h. The organic layer was then washed with 5% $NaHCO_3$ solution (3 x 15 cm^3). The combined aqueous

layers were extracted with dichloromethane (3 x 30 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated to give a mixture of the isomers (**3a**), (**4a**), and (**5a**) as a colourless liquid in almost quantitative yield in a respective ratio of 15 : 65 : 20 as determined by the integration of the benzylic protons at δ 5.10, 5.85 and 5.18, respectively. (In a separate experiment, efforts to separate the bridged hydroxylamine (**4a**) by silica gel chromatography using ethyl acetate as the eluant were unsuccessful. A mixture of tautomers (**3a**) and (**4a**) were obtained due to equilibration. Extensive decomposition occurred during chromatography).

To the above mixture of products (**3a**)-(**5a**) in dichloromethane (10 cm^3), was added methyl methacrylate (1.0 cm^3) and six drops of acetic acid. (It was presumed that the presence of acetic acid would increase the rate of conversion of the hydroxylamine (**4a**) to the nitrone (**3a**)). The reaction mixture was stirred at 20°C for 24 h. After removal of the solvent acetic acid and excess alkene, the residual mixture was separated by silica gel chromatography. Elution with ethyl acetate afforded the adduct *(2R*,3aS*,7S*)-methyl 7-[(2'S*)-2'-hydroxy-2'-phenyl]ethyl-2-methylperhydro-1,2-oxazolo[3,2-c][1,4]oxazine-2-carboxylate* (**6**) as white crystals (396 mg, 62.8%), m.p. 119-120°C (ether-dichloromethane) (Found : C, 63.4; H, 7.2; N, 4.1. $C_{17}H_{23}NO_5$ requires C, 63.53; H, 7.21; N, 4.36%); $\nu_{max.}$ (KBr) 3356, 3063, 3033, 2977, 2964, 2943, 2920, 1749, 1463, 1450, 1438, 1287, 1259, 1241, 1220, 1136, 768, and 690 cm^{-1}; δ_H 1.73 (2 H, m), 1.57 (3 H, s), 2.14 (1 H, dd, J 6.0, 12.0 Hz), 2.90 (1 H, t, J 12.0 Hz), 3.00-4.15 (7 H, m), 3.80 (3 H, s), 5.15 (1 H, t, J 7.0 Hz), and 7.30 (5 H, m); m/z 321 (M^+ 16.9%). Continued elution afforded a mixture of diastereomers (**7**) (58 mg, 9.2%) as colourless oil. The proton NMR spectra revealed the presence of the following major signals : δ_H 1.50 (3 H, s), 3.75 (3 H, s), and 4.95 (1 H, m).

Finally, the more substituted nitrone *2-(2'-hydroxy-2'-phenyl)ethyl-5,6-dihydro-1,4-oxazine 4-oxide* (**5a**) was eluted with 5 : 1 ethyl acetate-methanol mixture as colourless crystals (25 mg, 6.0%), m.p. 99-100°C (dichloromethane-ether) (Found : C, 64.9; H, 6.8; N, 6.15. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%), $\nu_{max.}$ (KBr) 3239, 2938, 2881, 1634, 1479, 1456, 1438, 1334, 1250, 1170, 1160, 1132, 766, and 708 cm^{-1}; δ_H 2.63 (1 H, dd, J 7.5, 14.0 Hz), 3.10 (1 H, dd, J 7.5, 14.0 Hz), 3.50-4.33 (6 H, m), 5.18 (1 H, dd, J 3.5, 7.5 Hz), 6.05 (1 H, br), and 7.30 (5 H, m); m/z 115 (M^+ - PhCHO, 100%).

(ii) in acetic acid : To a solution of the adduct (**2a**) (453 mg, 2.21 mmol) in acetic acid (8 cm^3), was added MCPBA (2.43 mmol) and the mixture was stirred at 20°C for 2 h. After removal of acetic acid by a stream of nitrogen, dichloromethane (10 cm^3) and methyl methacrylate (4 cm^3) were added to residual liquid and was stirred at 20°C for 24 h. After removal of solvent and excess alkene, the residual mixture was taken up in CH_2Cl_2 (30 cm^3) and washed with 5% $NaHCO_3$ solution (3 x 15 cm^3). The aqueous layer was reextracted with CH_2Cl_2 (3 x 30 cm^3). The combined organic layers was dried (Na_2SO_4), evaporated, and chromatographed as before to give the adducts (**6**) and (**7**) (30%) and the unreacted nitrone (**5a**) (55%). In a separate experiment in acetic acid, the mixture of ring opened products was isolated as described before and the integration of the benzylic protons revealed the presence of (**3a**)+(**4a**) and (**5a**) in a ratio of 35 : 65, respectively.

(iii) in methanol : The ring opening reaction was carried out in methanol using procedure as described under the reaction in dichloromethane and afforded the isomer (**3a**)+(**4a**) and (**5a**) in quantitative yield, in a respective ratio of 35 : 65.

Reaction of the Ring Opened Products (3a), (4a), and (5a) with Acetic Anhydride.- The mixture of the ring opened products (**3a**), (**4a**), and (**5a**), prepared by MCPBA oxidation of the adduct (**2a**) (303 mg, 1.48 mmol) in dichloromethane *(vide supra)*, was used without removal of the *m*-chlorobenzoic acid. The reaction mixture was concentrated to a volume of 10 cm^3 and acetic anhydride (2 cm^3) was added. After 24 h at 20°C, the solvent and excess acetic anhydride were removed by a stream of nitrogen. The residual mixture was chromatographed over basic alumina AG 10 (BIO-RAD, 100-200 mesh, activity IV) using 1 : 1 hexane/CH_2Cl_2 to give *(1R*,3S*,5S*)-9-acetoxy-3-phenyl-2,7-dioxa-9-azabicyclo[3,3,1] nonane* (**8**) (261 mg, 67%) as a colourless liquid which crystallizes in freezer as colourless plates, m.p. 92-93°C (ether-hexane) (Found : C, 63.8; H, 6.5; N, 5.2. $C_{14}H_{17}NO_4$ requires C, 63.86; H, 6.51; N, 5.32%); $\nu_{max.}$ (neat) 2960, 2872, 1762, 1456, 1363, 1219, 1132, 1077, 996, 919, 761, 732, and 706 cm^{-1}; δ_H 1.65-1.97 (1 H, m), 2.08 (3 H, s), 2.30-2.76 (1 H, m), 3.45 (1 H, m), 4.00-4.47 (4 H, m), 4.80 (1 H,

m), 5.88 (1 H, dd, J 4.5, 11.5 Hz), and 7.35 (5 H, m); m/z 263 (M^+ 28.9%). TLC experiment (alumina, CH_2Cl_2) revealed the presence of several spots with low R_f (0.0-0.1) values, but these compounds were not separated or analyzed.

Reduction of the Ring Opened Products (3a), (4a), and (5a) with Sodium Borohydride.- To a solution of the adduct **(2a)** (1.0 mmol) in methanol (15 cm^3), was added MCPBA (1.2 mmol). After stirring the reaction mixture for 30 min at 0°C, excess $NaBH_4$ (200 mg) was added and the stirring was continued for an additional 1 h at 20°C. After removal of the methanol, 25 cm^3 of 10% HCl solution was added to the residual mixture. The acid layer was washed with ether (3 x 15 cm^3) to remove *m*-chlorobenzoic acid. The acid layer was saturated with anhydrous K_2CO_3 and extracted with CH_2Cl_2 (3 x 25 cm^3). The organic layer was dried (Na_2SO_4), evaporated and chromatographed using ether as the eluant to give a non-separable mixture of the hydroxylamines *2-(2'-hydroxy-2-phenyl)ethyl-4-hydroxymorpholine* **(11)** and **(12)** as white solid (190 mg, 85%), m.p. 124-126°C (dichloromethane-ether) (Found : C, 64.3; H, 7.53; N, 6.15. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%); $\nu_{max.}$ (KBr) 3275, 2900, 2840, 1490, 1445, 1415, 1100, 1045, 977, 933, 838, 760, and 695 cm^{-1}; δ_H 1.53-2.38 (2 H, m), 2.55-4.16 (7 H, m), 4.57-5.09 (2 H, br), 4.98 (1 H, m), and 7.30 (5 H, m).

Mercury(II) Oxide Oxidation of the Hydroxylamines (11) and (12).- To a solution of the hydroxylamines **(11)** and **(12)** (50 mg, 0.224 mmol) in CH_2Cl_2 (3 cm^3) at 0°C, was added excess yellow HgO (250 mg, 1.15 mmol), and the reaction mixture was stirred for 30 min at 0°C during which the yellow HgO turned to grayish precipitate. Filtration of the reaction mixture through a small bed of $MgSO_4$ and evaporation afforded a mixture of nitrones **(3a)**, **(5a)**, and **(13)** as faint yellow liquid (47 mg, 95%). Initially, the ^1H NMR spectrum revealed the absence of the tautomer **(4a)**. However, the tautomer **(4a)** was present to the extent of 5% after 2 h, and equilibration was complete after 48 h, and it accounted for 30% of the total yield. The benzylic protons of **(3a)**, **(4a)**, **(5a)**, and **(13)** appeared, respectively, at δ 5.10 (dd, J 4.0, 8.0 Hz), 5.85 (dd, J 4.0, 12.0 Hz), 4.93 (dd, J 3.0, 10.0 Hz), and 5.10 (dd, J 4.0, 8.0 Hz) in a respective ratio of 7 : 30 : 56 : 7.

MCPBA Oxidation of the Adduct (2b) and Reaction of the Ring Opened Products with Styrene.-
(i) in dichloromethane : As described before, peracid oxidation of the adduct **(2b)** (390 mg, 2.46 mmol) in CH_2Cl_2 (30 cm^3) afforded a mixture of products **(3b)**, **(4b)**, and **(5b)**. However, the resulting reaction mixture was not soluble in CH_2Cl_2 due to its extreme polar nature, and was deposited on the wall of the flask. Addition of methanol (5 cm^3) made the reaction mixture homogeneous. After adding styrene (5 cm^3), the reaction mixture was heated to 50°C in a closed vessel for 24 h. After removal of the solvent and excess styrene, the crude residue was taken up in H_2O (10 cm^3) and washed with CH_2Cl_2 (4 x 20 cm^3). The unreacted nitrone **(5b)** remained in the aqueous layer. The solvent was removed from the aqueous layer at 35°C by blowing a stream of N_2, giving a brown oil which was purified by passing through a short silica gel column. Elution with 3 : 1 ethyl acetate-methanol mixture afforded the nitrone **(5b)** (44 mg, 10%) as a pale yellow liquid, $\nu_{max.}$ (neat) 3325, 2905, 2845, 1636, 1444, 1236, 1166, 1121, and 986 cm^{-1}; δ_H (CD_3OD) 2.33-3.00 (2 H, m), 3.25-4.33 (7 H, m), and 4.53 (2 H, m). The combined organic layers was stripped of the solvent, and the residue was taken up in 20 cm^3 10% aqueous HCl. The aqueous layer was washed with ether (3 x 15 cm^3) to remove *m*-chlorobenzoic acid. The aqueous layer was saturated with K_2CO_3 and extracted with CH_2Cl_2 (3 x 20 cm^3). The organic layer was dried (Na_2SO_4), and evaporated to give the adduct *(2S*,3aS*,7S*) 7-[(2'S*)-2',3'-dihydroxy]propyl-2-phenylperhydro-1,2-oxazolo[3,2-c][1,4] oxazine* **(9)** as a faint yellow liquid which was purified by passing through a short column using ethyl acetate as the eluant to give **(9)** as a colourless liquid (450 mg, 64.5%), (Found : C, 64.35 ; H, 7.40; N, 4.87. $C_{15}H_{21}NO_4$ requires C, 64.49; H, 7.58; N, 5.02%), $\nu_{max.}$ (neat) 3300, 2850, 1445, 1255, 1100, 912, and 752 cm^{-1}; δ_H 1.40-1.84 (2 H, m), 2.12 (1 H, ddd, J 4.0, 8.0, 12.0 Hz), 2.96 (1 H, q, J 12.0 Hz), 3.12-3.76 (7 H, m), 3.96 (4 H, m), 5.39 (1 H, dd, J 4.0, 9.5 Hz), and 7.35 (5 H, m); m/z 279 (M^+ 17.9%). We were unable to determine the composition of **(3b)**-**(5b)** from the ^1H n.m.r. spectrum. However, the ratio was determined by assuming quantitative isolation of the unreacted ketonitrone **(5b)** by chromatography.

(ii) in acetic acid : Peracid oxidation of the adduct **(2b)** in acetic acid was carried out using procedure as described before *(vide supra)*. After removal of acetic acid by a stream of N_2, the residual mixture

was reacted with styrene as described before to give the cycloaddition product (**9**) in 24% yield. As before, the unreacted more substituted nitrone (**5b**) was recovered from the aqueous layer (~65% yield).

Reaction of the Ring Opened Products (3b), (4b), and (5b), with Acetic Anhydride.- Ring opened products (**3b**)-(**5b**), obtained by MCPBA oxidation of the adduct (**2b**), were treated with acetic anhydride as described before. Purification of the reaction mixture by alumina chromatography using 1 : 1 ether/hexane as the eluant afforded *(1R*,3S*,5S*)-3-acetoxymethyl-9-acetoxy-2,7-dioxa-9-azabicyclo [3,3,1]nonane* (**10**) as a colourless liquid (32%), $\nu_{max.}$ (neat) 2975, 2882, 1760, 1743, 1367, 1237, 1220, 1138, 1091, 916, and 733 cm^{-1}; δ_H 1.40-1.70 (1 H, m), 2.10 (6 H, two closely spaced singlets), 2.20-2.50 (1 H, m), 3.40 (1 H, m), 3.55-4.40 (6 H, m), 4.70 (1 H, m), 4.88-5.25 (1 H, m).

MCPBA Oxidation of the Adduct (6).- Peracid oxidation of the adduct (**6**) in CH_2Cl_2, using the procedure as described before, afforded the crystalline nitrone *(6S*)-6-[(2'R*)-2'-carbomethoxy-2'-hydroxy]propyl-2-[(2'S*)-2'-hydroxy-2'-phenyl]ethyl-5,6-dihydro-1,4-oxazine 4-oxide* (**25**) as the sole regioisomer in quantitative yield, m.p. 136-138°C (dichloromethane-ether) (Found : C, 60.27; H, 6.90; N, 4.05. $C_{17}H_{23}NO_6$ requires C, 60.52; H, 6.87; N, 4.15%); $\nu_{max.}$ (KBr) 3300, 3163, 3012, 2948, 2836, 1736, 1650, 1438, 1216, 1191, 1150, 1054, 749, and 702 cm^{-1}; δ_H 1.48 (3 H, s), 1.87 (1 H, dd, J 4.5, 14.0 Hz), 2.46 (1 H, dd, J 8.0, 13.5 Hz), 2.86 (1 H, dd, J 8.0, 14.0 Hz), 3.02 (1 H, dd, J 3.5, 13.5 Hz), 3.80 (3 H, s), 3.85 (3 H, m), 4.10 (2 H, br s), 5.21 (1 H, dd, J 3.5, 8.0 Hz), 5.50 (2 H, br OH's), and 7.35 (5 H, m); m/z 231 (M^+ - PhCHO, 100%).

Peracid oxidation of the adduct (**6**) in methanol, as before, afforded a mixture of the nitrone (**25**) and (**26**) in quantitative yield in a respective ratio of 65 : 35. The C(2) methyl and benzylic protons of the minor isomer (**26**) appeared at δ 1.52 (s) and 5.04 (dd, J 4.0, 8.5 Hz), respectively.

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