Synthesis and Reactions of 1-[1-Oxido-2-(3,4)-pyridinyl]-2-methyloxiranes with Nitrogen Nucleophiles

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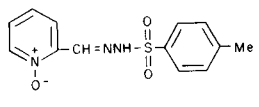
Received July 8, 1980

Reaction of 2(3,4)-pyridinecarboxaldehydes (**5**) with ethylidenetriphenylphosphorane afford a mixture of stereoisomers *Z*-(**6**) and *E*-1-[2(3,4)-pyridinyl]-1-propenes (**7**). *m*-Chloroperbenzoic acid oxidation of **6** and **7** yields a 60:40 mixture of *Z*-(**8**) and *E*-1-[1-oxido-2(3,4)-pyridinyl]-2-methyloxiranes (**9**). The regiospecific reaction of *Z*-isomers **8a-c** with cyclic amines as piperidine give rise to *threo*-1-hydroxy-1-[1-oxido-2(3,4)-pyridinyl]-2-(1-piperidino)propanes (**10**) while the *E*-isomer **9a** yields *erythro*-**11**. On tho other hand, the *E*-isomers **9b** and **9c** having 1-oxido-3(4)-pyridinyl substituents afford *erythro*-**12** resulting from attack by piperidine at C-1 of the oxirane. Reductive deoxygenation using 10% palladium on charcoal and hydrogen gas effectively removed the *N*-oxide substituent from the *threo*-**10** and *erythro*-**11** β-aminoalcohols. Dilute solution ir spectroscopy indicated the existance of strong intramolecular hydrogen bonding in the β-aminoalcohols **10** and **11**. The assignment of relative configuration of diastereoisomers **10** and **11** was based on the magnitude of the vicinal coupling constant J where J *threo* is greater than J *erythro*.

J. Heterocyclic Chem., **18**, 375 (1981).

There has recently been a considerable degree of pharmacological interest in arylsulfonylhydrazones of 2-formylpyridine *N*-oxide (**1**) and methenomycins (**2**) as antineoplastic agents (1,2). In an earlier report, we described the synthesis of 2- and 4-oxiranylpyridine 1-oxides and their reaction with nitrogen, oxygen and sulfur nucleophiles (3). It would, therefore, be of interest to extend this study to include the related oxiranes **8** and **9** for evaluation as antitumor agents and for reaction with amines to prepare previously inaccessible (4) heterocyclic analogs of adrenergic agents ephedrine (**3**) and ψ-ephedrine (**4**). We now describe the synthesis of *Z*-(**8**) and *E*-1-[1-oxido-2(3,4)-pyridinyl]-2-methyloxirane (**9**) and their reaction with nitrogen nucleophiles.



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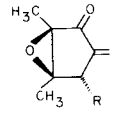
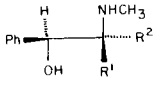
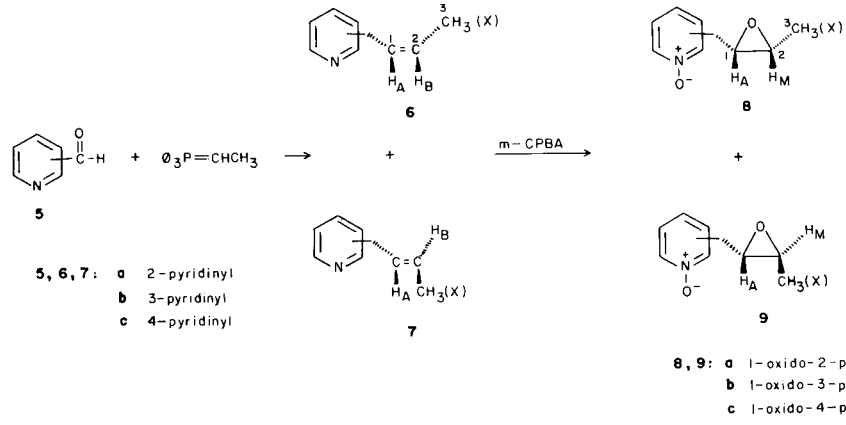


2 R = COOH, H



3; R^1 = H, R^2 = CH_3
4; R^1 = CH_3, R^2 = H

Reaction of 2-pyridinecarboxaldehyde **5a** with the Wittig reagent ethylidenetriphenylphosphorane afforded a 40:60 mixture (57.9%) of stereoisomers *Z*-(**6a**) and *E*-1-(2-pyridinyl)-1-propene (**7a**) which could not be separated by fractional distillation or column chromatography. The ^{1}H nmr spectrum of **6a** and **7a** exhibited a ABX_3 spin system for the 1-propene moiety which is very similar to that observed for *Z*- and *E*- isoeugenol (5). The ratio of **6a:7a** was determined by integration of the methyl absorptions which appeared respectively at δ 2.1 as a doublet (J_{BX} = 7 Hz) of doublets (J_{AX} = 1.5 Hz) and at δ 1.96 as a doublet (J_{AX} + J_{BX} = 5 Hz). Similar reactions of 3-pyridinecarboxaldehyde (**5b**) and 4-pyridinecarboxylaldehyde (**5c**) with ethylidenetriphenylphosphorane gave rise to the respective mixtures of stereoisomers **6b-7b** (70.8%) and **6c-7c** (78.9%). The ratio of **6b:7b** and **6c:7c** could not be calculated from the integration since the ABX_3 patterns of the two stereoisomers were superimposed upon one another.



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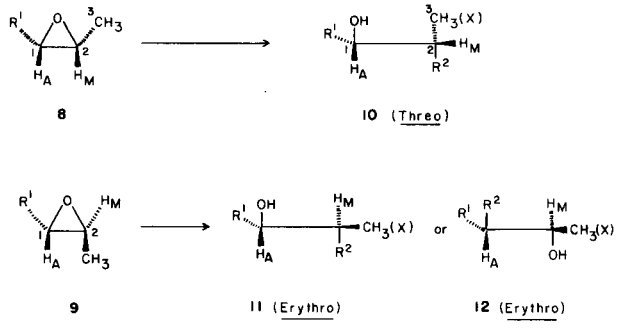
Oxidation of a mixture of *Z*-(**6a**) and *E*-1-(2-pyridinyl)-1-propene (**7a**) with excess *m*-chloroperbenzoic acid in methylene chloride afforded a 60:40 mixture (62.2%) of stereoisomers *Z*-(**8a**) and *E*-1-(1-oxido-2-pyridinyl)-2-methyloxirane (**9a**). Similar oxidation of olefins **6b-7b** and **6c-7c** gave rise to the respective mixtures of stereoisomers **8b-9b** (76.2%) and **8c-9c** (56.5%) also in ratios of about 60:40. It is interesting to note the epoxidation of **6b-7b** proceeds smoothly whereas epoxidation of 3-vinylpyridine afforded only a polymeric product believed to be poly-(3-vinylpyridine) and/or poly-(3-vinylpyridine 1-oxide) (6). The 2-methyloxirane moieties of **8** and **9** appeared as well resolved AMX_3 spin systems in the ^1H nmr spectrum. The observation that the ratio of oxiranes **8a-9a** obtained (60:40) is different from the ratio of olefins **6a-7a** (40:60) subjected to oxidation was not expected since epoxidation is a stereospecific reaction leading to a *cis*-addition of the oxygen atom to the double bond (7). This change in ratio could be due to differences in stability of **6a** and **7a** and/or **8a** and **9a** during the epoxidation reaction. The oxiranes **8** and **9** were relatively stable and were routinely purified by elution from a neutral alumina oxide column to remove excess *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid. Repeated attempts to separate **8** and **9** by fractional crystallization and column chromatography were unsuccessful although ratios of **8:9** as high as 80:20 were often obtained using the latter method.

The reaction of *Z* and *E*- oxiranes with nucleophiles as amines give rise to the respective *threo* (1*R*,2*R*/1*S*,2*S*) and *erythro* (1*R*,2*S*/1*S*,2*R*) β-aminoalcohol diastereoisomers (8-10). Thus, reaction of stereoisomers **8a** and **9a** (60:40 mixture) with piperidine at 80° for 8h gave a mixture of *threo*-(**10a**) and *erythro*-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(1-piperidino)propane (**11a**), respectively, in a ratio of 60:40 (75.8%). Diastereoisomers **10a** and **11a** were separated by fractional crystallization from acetone. The amination reaction was regiospecific since no product arising from attack by piperidine at C-1 of **8a** or **9a** was detected. Similar reactions were observed with morpholine and pyrrolidine (See Table 1).



The substituents R^1 and R^2 for **10-12** are as illustrated in Table 1.

On the other hand, amination of *Z*- and *E*-**8b-9b** and **8c-9c** having 1-oxido-3-pyridinyl and 1-oxido-4-pyridinyl substituents afforded a mixture of *threo*-**10** and *erythro*-**12** β-aminoalcohols (see Table 1). No trace of the *erythro*-**11** β-aminoalcohol was observed when ^1H nmr spectrum of the crude reaction product was recorded. In a related reaction, it was observed that a pure sample of *Z*-1-(1-oxido-4-pyridinyl)-2-methyloxirane (**8c**), obtained after repeated neutral alumina oxide column chromatography, on reaction with morpholine afforded *threo*-**10h** as the sole product. These results indicate that *Z*-oxiranes **8a-c** react with amines in both a regiospecific and stereospecific manner to give *threo*-**10** β-aminoalcohols whereas the *E*-oxiranes **9b-c** yield *erythro*-12 β-aminoalcohols arising from attack at C-1 of **9b-c**. The observation that reaction of the *E*-oxiranes **9a** with amines affords *erythro*-**11** rather than *erythro*-**12** is likely due to steric effects of the *N*-oxide substituent which precludes attack at C-1.

Reductive deoxygenation of *threo*-**10a** using 10% palladium-on-charcoal and hydrogen gas at 30 psi gave *threo*-1-hydroxy-1-(2-pyridinyl)-2-(1-piperidino)propane (**10j**) (54.2%) while deoxygenation of *erythro*-**11a** afforded *erythro*-**11j** (54.2%). The reductive deoxygenation of *threo*-**10** and *erythro*-**11** *N*-oxides is general and the results are summarized in Table 1.

Assignments of relative configurations to acyclic diastereoisomers is often based on the magnitude of the vicinal coupling constant J. In general J *erythro* is greater than J *threo* unless intramolecular hydrogen bonding exists where this factor may contribute more to conformational preferences than simple steric considerations in which case J *threo* would be greater than J *erythro* (5,8-10). It is therefore important to determine whether intramolecular hydrogen bonding exists in the β-aminoalcohols **10** and **11**. The ir spectra of **10j** and **11j** displayed broad absorptions corresponding to the bonded hydroxyl stretching bond. Dilute solution ir spectroscopy (11) showed a strong band at 3340 cm^{-1} for the *threo*-isomer **10j** and at 3425 cm^{-1} for the *erythro*-isomer **11j** down to a concentration of 0.005*M* (12). A free hydroxyl stretching band near 3500 cm^{-1} was not present in either spectrum which is indicative of a tightly intramolecularly bonded species. The bonded hydroxyl stretching bond did not change dramatically in intensity and in position thus providing evidence that diastereoisomers **10j** and **11j** are intramolecular hydrogen bonded in a non-polar solvent. In theory intramolecular hydrogen bonding in **10** and **11** could exist between the hydroxyl proton donor and either the *tertiary*-amino or pyridyl nitrogen electron-rich proton-acceptor functions. One would expect the intramolecular hydrogen bond of the former to be stronger since the basicity of the *tertiary*-amino nitrogen is greater than that of pyridyl nitrogen (11). Dilute solution infrared spectroscopy of **10r**, where intramolecular hydrogen bond-

Table 1

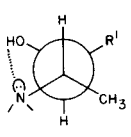
Some Synthetic and ^{1}H Nmr Data for the Products Obtained from the Reaction of *Z*-(**8**) and *E*-1-[1-Oxido-2(3,4)-pyridinyl]-2-methyloxirane (**9**) with Nucleophiles and the Deoxygenated Products *Threo*-(**10**) and *Erythro*-1-hydroxy-1-[2(3,4)-pyridinyl]-2-[1-piperidino(morpholino, pyrrolidino)]propane (**11**) (a)

10 (Threo) **11** (Erythro) **12** (Erythro)

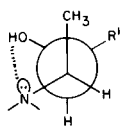
Epoxides	Nucleophile	R^1	R^2	Products	Isomer	% Yield	M.p., °C	Chemical Shifts H_A	H_M	CH_3	J_{AM}
8a and **9a**	piperidine	1-oxido-2-pyridinyl	1-piperidino	**10a**	*threo*	45.5	110-111	5.32	2.62 (b)	1.03	9
				11a	*erythro*	30.3	155-156	5.01	3.35	1.0	6.5
8a and **9a**	morpholine	1-oxido-2-pyridinyl	4-morpholino	**10b**	*threo*	31.5	152-153	5.35	2.72 (b)	1.06	9
				11b	*erythro*	24.5	164-165	5.08	3.34	1.0	5.75
8a and **9a**	pyrrolidine	1-oxido-2-pyridinyl	1-pyrrolidino	**10c**	*threo*	33.6	142-143	5.12	3.14	1.18	7
				11c	*erythro*	26.3	158-159	5.48	3.28	0.92	3.75
8b and **9b**	piperidine	1-oxido-3-pyridinyl	1-piperidino	**10d**	*threo*	49.9	97-99	4.22	2.52 (b)	0.86	9.5
				12d	*erythro*	21.8	144-147	3.06	4.35	1.06	5.5
8b and **9b**	morpholine	1-oxido-3-pyridinyl	4-morpholino	**10e**	*threo*	53.3	159-161	4.26	2.58 (b)	0.88	9
				12e	*erythro*	17	oil (c)	3.12	4.42	1.05	4.25
8b and **9b**	pyrrolidine	1-oxido-3-pyridinyl	1-pyrrolidino	**10f**	*threo*	34.6	123-124	4.23	2.7 (b)	0.88	9
				12f	*erythro*	trace (d)		2.96	4.28	1.03	3.5
8c and **9c**	piperidine	1-oxido-4-pyridinyl	1-piperidino	**10g**	*threo*	58.9	164-165	4.22	2.52 (b)	0.88	9
				12g	*erythro*	10.0	219-222	3.08	4.42	1.02	5
8c and **9c**	morpholine	1-oxido-4-pyridinyl	4-morpholino	**10h**	*threo*	44.0 (e)	150-151	4.30	2.56 (b)	0.88	9
				12h	*erythro*	13.7 (e)	158-159	3.14	4.42	1.08	4.5
8c and **9c**	pyrrolidine	1-oxido-4-pyridinyl	1-pyrrolidino	**10i**	*threo*	34.7	162-163	4.23	2.7 (b)	0.88	9
				12i	*erythro*	16.5	oil (c)	3.05	4.34	1.0	3.5
		2-pyridinyl	1-piperidino	**10j**	*threo*	54.2	51-52	4.42	2.62 (b)	0.88	9
				11j	*erythro*	54.2	solid (f)	4.98	2.95	0.90	4
		2-pyridinyl	4-morpholino	**10k**	*threo*	82.1	152-153	4.48	2.73 (b)	0.91	9
				11k	*erythro*	78.5	oil	5.01	2.87 (b)	0.88	4
		2-pyridinyl	1-pyrrolidino	**10l**	*threo*	79.1	oil (c)	4.62	3.26	1.06	9
				11l	*erythro*	62.9	166-167	5.22	3.28 (b)	0.92	3
		3-pyridinyl	1-piperidino	**10m**	*threo*	81.7	40-42	4.28	2.5 (b)	0.78	9
		3-pyridinyl	4-morpholino	**10n**	*threo*	81.4	58-59	4.35	2.68 (b)	0.86	9
		3-pyridinyl	1-pyrrolidino	**10o**	*threo*	79.8	38-40	4.3	2.86 (b)	0.78	9
		4-pyridinyl	1-piperidino	**10p**	*threo*	64.7	43-44	4.42	2.7 (b)	1.02	9
		4-pyridinyl	4-morpholino	**10q**	*threo*	80.3	92-94	4.25	2.58 (b)	0.84	9
		4-pyridinyl	1-pyrrolidino	**10r**	*threo*	61.8	93-94	4.26	2.8 (b)	0.85	9

(a) Spectra were obtained in deuteriochloroform. Chemical shifts are in δ units relative to tetramethylsilane; J are in hertz and all peaks had integrated areas appropriate to the structure. (b) H_M was coincident with the $-N\langle^{CH_2-}_{CH_2-}$ absorption. (c) Repeated attempts to crystallize **12** were unsuccessful. This product was very unstable. (d) The ^{1}H nmr spectrum of the residue remaining after removal of **10f** exhibited absorptions expected for **12f** but it could not be isolated. (e) These yields are only approximate since the separation of **10h** and **12h** was very difficult. (f) This product melts just above 25°.

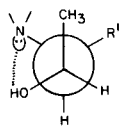
ing between the hydroxyl and pyridyl nitrogen is not expected to exist (13), also exhibited a strong intramolecular hydrogen bonded hydroxyl at 3375 cm^{-1} which did not change in intensity or position upon dilution (12). On this basis, one would expect the preferred conformations of the *threo*-**10** and *erythro*-**11** diastereoisomers to be **13** and **14**, respectively, in which the hydroxyl and R^2-substituent (piperidine, morpholine, pyrrolidine) are adjacent, and the bulkiest groups are *trans* to one another. In the *threo* isomer **13**, the protons have a *trans* relationship whereas in the *erythro* isomer **14** they are *gauche*. Since J *trans* is greater than J *gauche*, then for this series, J *threo* is greater than J *erythro* as shown in Table 1. The preferred conformation of *erythro*-**12** would then be **15** based on a vicinal coupling constant J_{AM} of 3.5-5.5 Hz (See Table 1).



13 (Threo)



14 (Erythro)



15 (Erythro)

Examination of the ^{1}H nmr data for products **10,11** and **12** shows that the *threo* and *erythro* isomers in this series can be identified from the chemical shift of H_A, H_M and the vicinal coupling constant J_{AM}.

We plan to prepare samples of **8** and **9a-c** for testing as potential anticancer agents.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in deuterochloroform (unless otherwise noted) with TMS as internal stan-

dard with a Varian EM-360A spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Unicam SP-1000 or Perkin Elmer 267 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer.

All of the products described gave rise to a single spot on tlc using a solvent system less polar and more polar than the specific solvent system described for purification of the reaction mixture. No residue remained after combustion of the products purified by chromatography.

Z-1-(2-Pyridinyl)-1-propene (**6a**) and *E*-1-(2-Pyridinyl)-1-propene (**7a**).

General Procedure.

A solution of *n*-butyllithium (5.72 g., 89.4 mmoles) in 39.7 ml. of hexane was added slowly with stirring during 10 minutes to a suspension of ethyltriphenylphosphonium bromide (35 g., 94.3 mmoles) in 180 ml. of dry tetrahydrofuran, under a nitrogen atmosphere at 25°. The resulting orange solution was allowed to stir for 30 minutes. A solution of 2-pyridinecarboxaldehyde (9.57 g., 89.4 mmoles) in 10 ml. of dry tetrahydrofuran was then added slowly with stirring during which a white precipitate starts separating and the reaction flask becomes warm. External cooling is used if required to keep the tetrahydrofuran below reflux temperature. The reaction mixture was allowed to stir at 25° for 60 hours, water (150 ml.) was added and stirring continued for 5 minutes. The organic layer was separated and the remainder of the reaction mixture was extracted with ether (3 × 75 ml.). The combined organic extracts were washed once with 50 ml. of water, once with brine and dried over sodium sulfate. Removal of the solvent *in vacuo* afforded a sticky residue which was extracted with petroleum ether (b.p. 37-51°, 60 ml.). Removal of the solvent gave a mixture of **6a** and **7a** (6.2 g., 57.9%) in a ratio of 40:60 as a pale yellow liquid, b.p. 70-75°/22 torr; ir (neat): 1655 and 1665 (s, CH = CH) cm^{-1}; ^1H nmr: δ 1.96 [d, $J_{AX} + J_{BX}$ = 5 Hz, 3H, Me (**7a**)], 2.1 [d, J_{BX} = 7 Hz of d, J_{AX} = 1.5 Hz, 3H, Me (**6a**)], 6.08 [m, 2H, H_B (**6a** and **7a**)], 6.68 [m, 2H, H_A (**6a** and **7a**)], 7.13 [m, 4H, H-3, H-5 (**6a** and **7a**)], 7.55 [m, 2H, H-4 (**6a** and **7a**)], 8.58 [m, 2H, H-6 (**6a** and **7a**)]; high resolution ms: exact mass calcd. for C_8H_9N: 119.0734; found: 119.0728.

Anal. Calcd. for C_8H_9N: C, 80.63; H, 7.61; H, 11.75. Found: C, 80.40; H, 7.70; N, 11.62.

Z-1-(3-Pyridinyl)-1-propene (**6b**) and *E*-1-(3-Pyridinyl)-1-propene (**7b**).

A solution of 3-pyridinecarboxaldehyde (10.4 g., 97 mmoles) in 10 ml. of dry tetrahydrofuran was added to a solution of ethylidenetriphenylphosphorane, prepared by addition of *n*-butyllithium (6.4 g., 100 mmoles) in 44.5 ml. of hexane to a suspension of ethyltriphenylphosphonium bromide (40 g., 107.7 mmoles) in 200 ml. of dry tetrahydrofuran as described under General Procedure A. The reaction was allowed to proceed for 96 hours to yield 8.18 g. (70.8%) of a mixture of **6b** and **7b** as a pale yellow liquid, b.p. 86-90°/22 torr; ir (neat): 1655 and 1670 (m, CH = CH) cm^{-1}; ^1H nmr: δ 1.86 (m, 3H, Me), 5.92 (m, 1H, H_B), 6.41 (m, 1H, H_A), 7.25 (d, $J_{4,5}$ = 8 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 7.62 (d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 2 Hz of d, $J_{2,4}$ = 2 Hz, 1H, H-4), 8.48 (d, $J_{5,6}$ = 5.0 Hz of d, $J_{4,6}$ = 2 Hz, 1H, H-6), 8.56 (d, $J_{2,4}$ = 2 Hz, 1H, H-2); high resolution ms: exact mass calcd. for C_8H_9N: 119.0734; found: 119.0732.

Anal. Calcd. for C_8H_9N: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.45; H, 7.65; N, 11.48.

Z-1-(4-Pyridinyl)-1-propene (**6c**) and *E*-1-(4-Pyridinyl)-1-propene (**7c**).

Reaction of 4-pyridinecarboxaldehyde (10.5 g., 98 mmoles) with the Wittig reagent ethylidenetriphenylphosphorane (100 mmoles) and completion of the reaction as described under General Procedure A gave a mixture of **6c** and **7c** (9.2 g., 78.9%) as a pale yellow liquid; b.p. 97-106°/20 torr; ir (neat): 1645 and 1655 (m, CH = CH) cm^{-1}; ^1H nmr: δ 1.9 (m, 3H, Me), 6.06 (m, 1H, H_B), 6.58 (m, 1H, H_A), 7.16 (d, $J_{2,3} = J_{5,6}$ = 6 Hz, 2H, H-3, H-5), 8.58 (d, $J_{2,3} = J_{5,6}$ = 6 Hz, 2H, H-2, H-6); high resolution ms: exact mass calcd. for C_8H_9N: 119.0734; found: 119.0730.

Anal. Calcd. for C_8H_9N: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.36; H, 7.74; N, 11.51.

Z-1-(1-Oxido-2-pyridinyl)-2-methyloxirane (**8a**) and *E*-1-(1-Oxido-2-pyridinyl)-2-methyloxirane (**9a**).

General Procedure B.

A solution of *Z*-(**6a**) and *E*-1-(2-pyridinyl)-1-propene (**7a**) (3.5 g., 29.4 mmoles) in 10 ml. of dry methylene chloride was added all at once to a suspension of *m*-chloroperbenzoic acid (17.48 g. of 85%, 86.1 mmoles) in 150 ml. of dry methylene chloride with stirring at 0°. The reaction mixture was subsequently stirred for 30 minutes at 0°, for 12 hours at 25° and for 24 hours at reflux temperature. The reaction mixture was cooled to 25° and filtered to remove the solid material present. The filtrate was concentrated and filtered again to remove the solid material present. Removal of the solvent from the filtrate *in vacuo* gave a viscous oil. Elution of this product from a neutral alumina column (90 g.) using 200 ml. of chloroform afforded a mixture of **8a** and **9a** (2.7 g., 62.2%) in a ratio of 60:40 as a viscous light yellow oil; ir (neat): 1265 (s, *N*-oxide) cm^{-1}; ^1H nmr: δ (stereoisomer **8a**) 1.12 (d, J_{MX} = 5.5 Hz, 3H, Me), 3.62 (d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 4.5 Hz, 1H, H_M), 4.48 (d, J_{AM} = 4.5 Hz, 1H, H_A), 7.3 (m, 3H, H-3, H-4, H-5), 8.3 (m, 1H, H-6) (stereoisomer **9a**) 1.55 (d, J_{MX} = 5.5 Hz, 3H, Me), 3.0 (d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 2 Hz, 1H, H_M), 4.32 (d, J_{AM} = 2 Hz, 1H, H_A), 7.3 (m, 3H, H-3, H-4, H-5), 8.3 (m, 1H, H-6); high resolution ms: exact mass calcd. for $C_8H_9NO_2$: 151.0633; found: 151.0633.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.43; H, 6.14; N, 9.03.

Z-1-(1-Oxido-3-pyridinyl)-2-methyloxirane (**8b**) and *E*-1-(1-Oxido-3-pyridinyl)-2-methyloxirane (**9b**).

Oxidation of a mixture of *Z*-(**6b**) and *E*-1-(3-pyridinyl)-1-propene (**7b**) (5.7 g., 47.9 mmoles) using *m*-chloroperbenzoic acid (28.5 g. of 85%, 140.4 mmoles) and completion of the reaction as described under General Procedure B afforded a viscous oil which was purified using a neutral alumina oxide column (120 g.). Elution with 150 ml. of benzene gave some undesired material which was not examined further. Further elution with benzene-methanol (5:1 v/v, 250 ml.) afforded a mixture of **8b** and **9b** (5.51 g., 76.2%) in a ratio of 60:40 as a pale yellow viscous oil; ir (neat): 1260 (s, *N*-oxide) cm^{-1}; ^1H nmr: δ (stereoisomer **8b**) 1.2 (d, J_{MX} = 5.5 Hz, 3H, Me), 3.5 (d, J_{MX} = 5.5 Hz, of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 4.5 Hz, 1H, H_M), 4.1 (d, J_{AM} = 4.5 Hz, 1H, H_A), 7.25 (m, 2H, H-4, H-5), 8.2 (m, 2H, H-2, H-6) (stereoisomer **9b**) 1.52 (d, J_{MX} = 5.5 Hz, 3H, Me), 3.12 (d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 2 Hz, 1H, H_M), 3.68 (d, J_{AM} = 2 Hz, 1H, H_A), 7.25 (m, 2H, H-4, H-5), 8.2 (m, 2H, H-2, H-6); high resolution ms: exact mass calcd. for $C_8H_9NO_2$: 151.0633; found: 151.0633.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.36; H, 6.24; N, 9.17.

Z-1-(1-Oxido-4-pyridinyl)-2-methyloxirane (**8c**) and *E*-1-(1-Oxido-4-pyridinyl)-2-methyloxirane (**9c**).

Oxidation of a mixture of *Z*-(**6c**) and *E*-1-(4-pyridinyl)-1-propene (**7c**) (6.37 g., 53.5 mmoles) using *m*-chloroperbenzoic acid (31.85 g. of 85%, 157 mmoles) and completion of the reaction as described under General Procedure B yielded a viscous oil. Elution from a neutral alumina oxide column (130 g.) using 350 ml. of benzene as eluant gave 4.57 g. (56.5%) of **8c** and **9c** in a ratio of 60:40, as determined from the integrals of the respective methyl absorptions at δ 1.08 and 1.4, as a pale yellow viscous oil; ir (neat): 1240 (s, *N*-oxide) cm^{-1}; ^1Hnmr δ (stereoisomer **8c**) 1.08 (d, J_{MX} = 5.5 Hz, 3H, Me), 3.4 (d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 4.5 Hz, 1H, H_M), 4.02 (d, J_{AM} = 4.5 Hz, 1H, H_A), 7.25 (m, 2H, H-3, H-5), 8.32 (d, $J_{2,3} = J_{5,6}$ = 7 Hz, 2H, H-2, H-6) (stereoisomer **9c**) 1.4 (d, J_{MX} = 5.5 Hz, 3H, Me), 2.92 (d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{MX} = 5.5 Hz of d, J_{AM} = 2 Hz, 1H, H_M), 3.52 (d, J_{AM} = 2 Hz, 1H, H_A), 7.25 (m, 2H, H-3, H-5), 8.3 (d, $J_{2,3} = J_{5,6}$ = 7 Hz, 2H, H-2, H-6); high resolution ms: exact mass calcd. for $C_8H_9NO_2$: 151.0633; found: 151.0634.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.50; H, 6.06; N, 9.40.

Threo-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(1-piperidino)propane (**10a**) and *Erythro*-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(1-piperidino)propane (**11a**).

General Procedure C.

Reaction of a 60:40 mixture of stereoisomers *Z*-(**8a**) and *E*-1-(1-oxido-2-pyridinyl)-2-methyloxirane (**9a**) (1.34 g., 8.87 mmoles) with piperidine (2.15 g., 25.3 mmoles) at 80° for 8 hours and removal of excess piperidine *in vacuo* afforded a dark semi-solid product. Trituration with 25 ml. of acetone gave 0.388 g. of nearly pure **11a**. The acetone soluble material was purified by elution from a neutral alumina oxide column (30 g.) using ethyl acetate-methanol (1:1 v/v, 500 ml.) to yield 1.207 g. of additional **10a** and **11a** for a combined weight of 1.595 g. (75.8%). The ratio of **10a:11a** which was determined by integration of H_A at 5.32 and 5.01 δ in the respective products was 3:2. The isomers were separated by fractional crystallization from acetone. The *erythro* isomer **11a**, being less soluble in acetone, was obtained in the first crops of crystals.

Diasterioisomer **10a**.

This compound had ^{1}H nmr: δ 1.03 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.58 (m, 6H, piperidino H-3, H-4, H-5), 2.2-3.0 (m, 5H, H_M, piperidino H-2, H-6), 5.05 (br s, 1H, -OH, exchanges with deuterium oxide), 5.32 (d, J_{AM} = 9 Hz, 1H, H_A), 7.0-7.7 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.2 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.53; N, 11.86. Found: C, 65.67; H, 8.33; N, 11.35.

Diasterioisomer **11a**.

This compound had ir: 1220 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 1.0 (d, J_{MX} = 7 Hz, 3H, Me), 1.42 (m, 6H, piperidino H-3, H-4, H-5), 2.58 (m, 4H, piperidino H-2, H-6), 3.35 (d, J_{MX} = 7 Hz of d, J_{MX} = 7 Hz of d, J_{MX} = 7 Hz of d, J_{AM} = 6.5 Hz, 1H, H_M), 5.01 (d, J_{AM} = 6.5 Hz, 1H, H_A), 5.54 (br s, 1H, -OH, exchanges with deuterium oxide), 7.0-7.6 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.16 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.53; N, 11.86. Found: C, 65.66; H, 8.58; N, 11.59.

Threo-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(4-morpholino)propane (**10b**) and *Erythro*-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(4-morpholino)propane (**11b**).

Reaction of a mixture of **8a** and **9a** (1.17 g., 7.7 mmoles) with morpholine (2.31 g., 26.6 mmoles) at 80° for 8 hours and removal of excess morpholine *in vacuo* gave a dark semi-solid product. Repeated trituration of the product with acetone afforded 1.03 g. (56%) of **10b** and **11b** in a ratio of 13:10 as determined by integration of H_A at δ 5.35 and 5.08 in the respective products. Fractional crystallization from acetone was used to obtain pure samples of each diastereoisomer. The less soluble **11b** appeared in the first crop of crystals.

Diastereoisomer (**10b**).

This compound had ir: 1215 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 1.06 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.3-3.1 (m, 5H, H_M, morpholino H-3, H-5), 3.8 (m, 4H, morpholino H-2, H-6), 5.16 (s, 1H, -OH, exchanges with deuterium oxide), 5.35 (d, J_{AM} = 9 Hz, 1H, H_A, 7.16-7.8 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.26 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 60.47; H, 7.62; N, 11.76. Found: C, 60.57; H, 7.74; N, 11.58.

Diastereoisomer **11b**.

This compound had ir: 1230 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 1.0 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.63 (m, 4H, morpholino H-3, H-5), 3.34 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 5.75 Hz, 1H, H_M), 3.6 (m, 4H, morpholino H-2, H-6), 5.08 (d, J_{AM} = 5.75 Hz, 1H, H_A), 5.35 (br s, 1H, -OH, exchanges with deuterium oxide), 7.1-7.6 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.2 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.47; H, 7.62; N, 11.76. Found: C, 60.13; H, 7.68; N, 11.45.

Threo-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(1-pyrrolidino)propane (**10c**) and *Erythro*-1-hydroxy-1-(1-oxido-2-pyridinyl)-2-(1-pyrrolidino)propane (**11c**).

A mixture of oxiranes **8a** and **9a** (1.1 g., 7.28 mmoles) and pyrrolidine (1.95 g., 27.2 mmoles) was heated at 80° for 8 hours and the excess pyrrolidine was removed *in vacuo* to yield a dark semi-solid product. Repeated trituration of the product with acetone afforded 0.97 g. (59.9%) of **10c** and **11c** in a ratio of 14:11 as determined by integration of H_A δ at 5.12 and 5.48 for the respective products. Fractional crystallization of this mixture from acetone gave the less soluble isomer **11c** in the first crops of crystals.

Diastereoisomer **10c**.

This compound had ir: 1220 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 1.18 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.76 (m, 4H, pyrrolidino H-3, H-4), 2.66 (m, 4H, pyrrolidino H-2, H-5), 3.14 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 7 Hz, 1H, H_M), 5.12 (d, J_{AM} = 7 Hz, 1H, H_A), 5.36 (br s, 1H, OH, exchanges with deuterium oxide), 7.0-7.8 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.25 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.64; H, 8.19; N, 12.45.

Diastereoisomer **11c**.

This compound had ir: 1215 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 0.92 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.82 (m, 4H, pyrrolidino H-3, H-4), 2.78 (m, 4H, pyrrolidino H-2, H-5), 3.28 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 3.75 Hz, 1H, H_M), 4.95 (br s, 1H, OH, exchanges with deuterium oxide), 5.48 (d, J_{AM} = 3.75 Hz, 1H, H_A), 7.0-7.8 (m, 3H, H-3, H-4, H-5 of pyridine 1-oxide), 8.25 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.48; H, 8.18; N, 12.74.

Threo-1-hydroxy-1-(1-oxido-3-pyridinyl-2-(1-piperidino)propane (**10d**) and *Erythro*-2-hydroxy-1-(1-oxido-3-pyridinyl)-1-(1-piperidino)propane (**12d**).

Reaction of a mixture of oxiranes **8b** and **9b** (1.49 g., 9.86 mmoles) with piperidine (2.58 g., 30.4 mmoles) at 80° for 8 hours and removal of the excess piperidine *in vacuo* afforded a dark semisolid product. Trituration with 25 ml. of acetone gave 0.343 g. of nearly pure **12d**. The acetone soluble material was purified by elution from a neutral alumina oxide column (60 g.) using 250 ml. of methanol-ethyl acetate (1:9 v/v) to yield 1.33 g. of additional **10d** and **12d** for a combined weight of 1.673 g. (70.7%). The ratio of **10d:12d** which was determined from the integrals of H_A at δ 4.22 and 3.06 in the respective products was 16:7. Fractional crystallization of the mixture obtained above by alumina oxide column chromatography from acetone gave **10d** as a pale yellow crystalline solid; ir: 1235 (s, *N*-oxide) and 3240 (s, OH) cm^{-1}; ^{1}H nmr: δ 0.86 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.6 (m, 6H, piperidino H-3, H-4, H-5), 2.52 (m, 5H, H_M, piperidino H-2, H-6), 4.22 (d, J_{AM} = 9.5 Hz, 1H, H_A), 5.46 (br, s, 1H, OH, exchanges with deuterium oxide), 7.3 (m, 2H, H-4, H-5 of pyridine-1-oxide), 8.18 (d, J_{56} = 6 Hz of d, J_{46} = 2 Hz, 1H, H-6), 8.28 (d, J_{24} = 2 Hz, 1H, H-2).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.53; N, 11.86. Found: C, 66.18; H, 8.50; N, 11.81.

Recrystallization of the sample of **12d**, obtained by trituration, from acetone gave a pure sample of **12d**; ir: 1255 (s, *N*-oxide) and 3200 (s, OH) cm^{-1}; ^{1}H nmr: 1.06 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.46 (m, 6H, piperidino H-3, H-4, H-5), 2.4 (m, 4H, piperidino H-2, H-6), 3.06 (d, J_{AM} = 5.5 Hz, 1H, H_A), 3.75 (br s, 1H, OH, exchanges with deuterium oxide), 4.35 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 5.5 Hz, 1H, H_M), 7.28 (m, 2H, H-4, H-5 of pyridine 1-oxide), 8.16 (m, 2H, H-2, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.18; H, 8.50; N, 11.81. Found: C, 65.89; H, 8.45; N, 11.60.

Threo-1-hydroxy-1-(1-oxido-3-pyridinyl)-2-(4-morpholino)propane (**10e**) and *Erythro*-2-hydroxy-1-(1-oxido-3-pyridinyl)-1-(4-morpholino)propane (**12e**).

A mixture of oxiranes **8b** and **9b** (0.67 g., 4.4 mmoles) and morpholine (1.51 g., 17.3 mmoles) was heated at 80° for 8 hours and the excess morpholine was removed *in vacuo* to yield a dark orange viscous oil. Crystallization from 15 ml. of acetone gave 0.407 g. of **10e**. Concentration of the mother liquor gave another 0.156 g. of **10e** as light yellow crystals (53.3%); ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.58 (m, 5H, H_M, morpholino H-3, H-5), 3.8 (m, 4H, morpholino H-2, H-6), 4.26 (d, J_{AM} = 9 Hz, 1H, H_A), 5.1 (br s, 1H, OH, exchanges with deuterium oxide), 7.28 (m, 2H, H-4, H-5 of pyridine 1-oxide), 8.12 (d, $J_{5,6}$ = 6 Hz of d, $J_{4,6}$ = 2 Hz, 1H, H-6 of pyridine 1-oxide), 8.28 (d, $J_{2,4}$ = 2 Hz, 1H, H-2 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.47; H, 7.62; N, 11.76. Found: C, 60.16; H, 7.63; N, 11.39.

The mother liquor from the second recrystallization described above was purified by elution from two consecutive neutral alumina oxide columns using 250 ml. of methanol-ethyl acetate (1:9 v/v) to afford **12e** (0.18 g., 17%) as a very unstable viscous oil. Repeated attempts to obtain a crystalline sample and a satisfactory elemental analyses were not successful. ^{1}H nmr: δ 1.05 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.5 (m, 4H, morpholino H-3, H-5), 3.12 (d, J_{AM} = 4.25 Hz, 1H, H_A), 3.72 (m, 4H, morpholino H-2, H-6), 4.42 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 4.25 Hz, 1H, H_M), 4.58 (br s, 1H, OH, exchanges with deuterium oxide), 7.35 (m, 2H, H-4, H-5 of pyridine 1-oxide), 8.1-8.48 (m, 2H, H-2, H-6 of pyridine 1-oxide); ms (chemical ionization, ammonia): M + 1 (239) and 2M + 1 (477).

Threo-1-hydroxy-1-(1-oxido-3-pyridinyl)-2-(1-pyrrolidino)propane (**10f**) and *Erythro*-2-hydroxy-1-(1-oxido-3-pyridinyl)-1-(1-pyrrolidino)propane (**12f**).

Reaction of a mixture of oxiranes **8b** and **9b** (0.99 g., 6.5 mmoles) with pyrrolidine (1.7 g., 23.6 mmoles) at 80° for 8 hours and removal of the excess pyrrolidine *in vacuo* gave a dark semi-solid product. Crystallization from 10 ml. of acetone afforded 0.508 g. of **10f** (34.6%) as pale yellow crystals; ir: 1260 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me),.1.8 (m, 4H, pyrrolidino H-3, H-4), 2.42-3.1 (m, 5H, H_M, pyrrolidino H-2, H-5), 4.23 (d, J_{AM} = 9 Hz, 1H, H_A), 5.0 (br s, 1H, OH, exchanges with deuterium oxide), 7.25 (m, 2H, H-4, H-5 of pyridine-1-oxide), 8.06-8.36 (m, 2H, H-2, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.48; H, 8.26; N, 12.34.

The ^{1}H nmr spectrum of the mother liquor described above exhibited absorptions expected for **12f**, but it could not be isolated (see Table 1).

Threo-1-hydroxy-1-(1-oxido-4-pyridinyl)-2-(1-piperidino)propane (**10g**) and *Erythro*-2-hydroxy-1-(1-oxido-4-pyridinyl)-1-(1-piperidino)propane (**12g**).

A mixture of oxiranes **8c** and **9c** (1.99 g., 13.17 mmoles) and piperidine (3.44 g., 40.5 mmoles) was heated at 80° for 8 hours and the excess piperidine was removed *in vacuo* to afford a dark semi-solid. The product was triturated with 50 ml. of acetone, stored in the freezer for 12 hours, and then filtered to yield 1.934 g. of a solid. Concentration of the mother liquor and storing in the freezer for 12 hours gave an additional 0.208 g. of product for a combined weight of 2.142 g. This solid material was stirred in 100 ml. of boiling acetone and filtered to remove the insoluble material (0.46 g.) which on recrystallization from methanol gave **12g** (0.312 g., 10%) as a yellow crystalline solid; ir: 1220 (s, *N*-oxide) and 3200 (s, OH) cm^{-1}; ^{1}H nmr (methanol-d_4): δ 1.02 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.55 (m, 6H, piperidino H-3, H-4, H-5), 2.4 (m, 4H, piperidino H-2, H-6), 3.08 (d, J_{AM} = 5 Hz, 1H, H_A), 3.3 (broad s, 1H, OH, exchanges slowly with deuterium oxide), 4.42 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 5 Hz, 1H, H_M), 7.52 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.36 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.53, N, 11.86. Found: C, 65.68; H, 8.53; N, 11.86.

Concentration of the acetone mother liquor after removal of **12g** as described above and cooling in the freezer for 12 hours gave **10g** (0.9 g.) as a pale yellow crystalline solid; ir: 1235 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.6 (m, 6H, piperidino H-3, H-4, H-5), 2.52 (m, 5H, H_M, piperidino H-2, H-6), 4.22 (d, J_{AM} = 9 Hz, 1H, H_A), 5.45 (broad s, 1H, OH, exchanges with deuterium oxide), 7.34 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.26 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.53; N, 11.86. Found: C, 65.86; H, 8.35; N, 11.97.

Threo-1-hydroxy-1-(1-oxido-4-pyridinyl)-2-(4-morpholino)propane (**10h**) and *Erythro*-2-hydroxy-1-(1-oxido-4-pyridinyl)-1-(4-morpholino)propane (**12h**).

Reaction of a mixture of oxiranes **8c** and **9c** (2.01 g., 13.3 mmoles) and morpholine (4.03 g., 46.2 mmoles) at 80° for 8 hours and removal of excess morpholine *in vacuo* gave a dark semi-solid product. This product on recrystallization from acetone gave a first crop of crystals consisting primarily of **10h** (0.192 g.) as well as a second (0.808 g.) and a third crop (0.192 g.) which were comprised of a mixture of **10h** and **12h**. The acetone mother liquor was purified by elution from a silica gel column (30 g.). Elution with 100 ml. of ethyl acetate gave some material which was not of interest while elution with ethyl acetate-methanol (4:1 v/v, 200 ml.) gave a further 0.616 g. of **10h** and **12h** for a total weight of 1.808 g. (57.76%). Pure samples of **10h** and **12h** were obtained by fractional recrystallization from acetone. The yields of **10h** and **12h** were calculated from the ratios of the integrals for the H_A protons at δ 4.3 and 3.14 and were found to be about 44% and 13.7%, respectively.

Threo-**10h**.

This compound had ir: 1225 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.1-3.0 (m, 5H, H_M, morpholino H-3, H-5), 3.8 (m, 4H, morpholino H-2, H-6), 4.3 (d, J_{AM} = 9 Hz, 1H, H_A), 5.15 (broad s, 1H, OH, exchanges slowly with deuterium oxide), 7.35 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.22 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.47; H, 7.62; N, 11.76. Found: C, 60.25; H, 7.65; N, 11.95.

Erythro-**12h**.

This compound had ir: 1250 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 1.08 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.18-2.88 (m, 4H, morpholino H-3, H-5), 3.14 (d, J_{AM} = 4.5 Hz, 1H, H_A), 3.78 (m, 4H, morpholino H-2, H-6), 4.42 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 4.5 Hz, 1H, H_M), 4.9 (broad s, 1H, OH, exchanges with deuterium oxide), 7.36 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.2 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide); ms (chemical ionization, ammonia): M + 1 (239), 2M + 1 (477). Repeated attempts to obtain a satisfactory elemental analyses were not successful.

Threo-1-hydroxy-1-(1-oxido-4-pyridinyl)-2-(1-pyrrolidino)propane (**10i**) and *Erythro*-2-hydroxy-1-(1-oxido-4-pyridinyl)-1-(1-pyrrolidino)propane (**12i**).

A mixture of oxiranes **8c** and **9c** (1.9 g., 12.5 mmoles) and pyrrolidine (2.13 g., 29.5 mmoles) was heated at 80° for 8 hours and the excess pyrrolidine was removed *in vacuo* to yield a semi-solid product. Recrystallization from acetone gave 0.967 g. (34.7%) **10i** as pale yellow crystals; ir: 1240 (s, *N*-oxide) cm^{-1}; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.82 (m, 4H, pyrrolidino H-3, H-4), 2.7 (m, 5H, H_M, pyrrolidino H-2, H-5), 4.23 (d, J_{AM} = 9 Hz, 1H, H_A), 5.3 (broad s, 1H, OH, exchanges with deuterium oxide), 7.34 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.22 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.72; H, 8.13; N, 12.37.

The mother liquor from above was purified by elution from two consecutive silica gel columns (30 g.) using 300 ml. of methanol-ethyl acetate (1:4 v/v) as eluant to afford 0.46 g. (16.5%) **12i** as an oil which was very

unstable. Repeated attempts to crystallize **12i** and to obtain a satisfactory elemental analyses were not successful; ^{1}H nmr: δ 1.0 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.83 (m, 4H, pyrrolidino H-3, H-4), 2.68 (m, 4H, pyrrolidino H-2, H-5), 3.05 (d, J_{AM} = 3.5 Hz, 1H, H_A), 4.34 (m, d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 3.5 Hz, 1H, H_M), 4.45 (broad s, 1H, OH, exchanges with deuterium oxide), 7.38 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-3, H-5 of pyridine 1-oxide), 8.25 (d, $J_{2,3}$ = $J_{5,6}$ = 7 Hz, 2H, H-2, H-6 of pyridine 1-oxide); ms (chemical ionization, ammonia): M + 1 (223) and 2M + 1 (445).

Threo-1-hydroxy-1-(2-pyridinyl)-2-(1-piperidino)propane (**10j**).

General Procedure. D

Reductive deoxygenation of **10a** (0.50 g., 2.12 mmoles) in absolute ethanol (45 ml.) was effected using 10% palladium-on-charcoal (0.15 g.) and hydrogen gas at 30 psi for 12 hours. Removal of the catalyst by filtration, evaporation of the solvent *in vacuo* and purification by elution from a silica gel column (20 g.) using 250 ml. of ethyl acetate gave 0.27 g. of **10j** (54.2%) as yellow crystals; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.6 (m, 6H, piperidino H-3, H-4, H-5), 2.2-3.0 (m, 5H, H_M, piperidino H-2, H-6), 4.42 (d, J_{AM} = 9 Hz, 1H, H_A), 5.2 (sharp s, 1H, OH, exchanges slowly with deuterium oxide), 7.05-7.9 (m, 3H, H-3, H-4, H-5 of pyridine), 8.6 (d, $J_{5,6}$ = 5 Hz, of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine).

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.86; H, 9.16; N, 12.72. Found: C, 71.2; H, 9.35; N, 12.58.

Erythro-1-hydroxy-1-(2-pyridinyl)-2-(1-piperidino)propane (**11j**).

Deoxygenation of **11a** (0.345 g., 1.46 mmoles) in absolute ethanol (45 ml.) using 0.13 g of 10% palladium-on-charcoal and completion of the reaction as described under General Procedure D including silica gel column purification afforded **11j** (0.187 g., 54.2%); ^{1}H nmr: δ 0.90 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.57 (m, 6H, piperidino H-3, H-4, H-5), 2.68 (m, 4H, piperidino H-2, H-6), 2.95 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 4 Hz, 1H, H_M), 4.60 (sharp s, 1H, OH, exchanges with deuterium oxide), 4.98 (d, J_{AM} = 4 Hz, 1H, H_A), 7.06-7.9 (m, 3H, H-3, H-4, H-5 of pyridine), 8.56 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, H-6 of pyridine); high resolution ms: exact mass calcd. for $C_{13}H_{20}N_2O$: 220.1575; found: 220.1561.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.86; H, 9.16. Found: C, 70.27; H, 9.19.

Threo-1-hydroxy-1-(2-pyridinyl)-2-(4-morpholino)propane (**10k**).

Deoxygenation of **10b** (0.15 g., 0.63 mmole) in absolute ethanol (25 ml.) using 0.05 g. of 10% palladium-on-charcoal, completion of the reaction as described under Procedure D and elution of the product from a neutral alumina oxide column (7 g.) using 30 ml. of ethyl acetate as eluant afforded **10k** (0.115 g., 82.1%); ^{1}H nmr: δ 0.91 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.3-3.1 (m, 5H, H_M, morpholino H-3, H-4), 3.85 (m, 4H, morpholino H-2, H-5), 4.48 (d, J_{AM} = 9 Hz, 1H, H_A), 4.92 (broad s, 1H, OH, exchanges with deuterium oxide), 7.1-7.9 (m, 3H, H-3, H-4, H-5 of pyridine), 8.68 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.01; H, 8.16; N, 12.37.

Repeated attempts to get a satisfactory elemental for carbon were not successful; ms (chemical ionization, ammonia): M + 1 (207).

Erythro-1-hydroxy-1-(2-pyridinyl)-2-(4-morpholino)propane (**11k**).

Reductive deoxygenation of **11b** (0.13 g., 0.546 mmole) in absolute ethanol (25 ml.) using 0.05 g. of 10% palladium-on-charcoal, completion of the reduction as described under Procedure D and purification of the product by elution from a neutral alumina oxide column (5 g.) using 20 ml. of ethyl acetate-methanol (4:1 v/v) as eluant afforded **11k** (0.095 g., 78.5%) as an oil; ^{1}H nmr: δ 0.88 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.5-3.0 (m, 5H, H_M, morpholino H-3, H-5), 3.78 (m, 4H, morpholino H-2, H-6), 4.17 (broad s, 1H, OH, exchanges slowly with the deuterium oxide), 5.01 (d, J_{AM} = 4 Hz, 1H, H_A), 7.05-7.95 (m, 3H, H-3, H-4, H-5 of pyridine), 8.57 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine); high resolution ms: exact mass calcd. for $C_{12}H_{18}N_2O$: 222.1358; found: 222.1363.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.43; H, 8.25; N, 12.49.

Threo-1-hydroxy-1-(2-pyridinyl)-2-(1-pyrrolidino)propane (**10l**).

Deoxygenation of **10c** (0.15 g., 0.675 mmole) in 25 ml. of absolute ethanol using 0.05 g. of 10% palladium-on-charcoal, and completion of the reaction as described under Procedure D gave 0.11 g. of **11l** (79.1%) as an unstable oil; ^{1}H nmr: δ 1.06 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.0 (m, 4H, pyrrolidino H-3, H-4), 2.9 (m, 4H, pyrrolidino H-2, H-5), 3.26 (d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{MX} = 6.5 Hz of d, J_{AM} = 9 Hz, 1H, H_M), 4.62 (d, J_{AM} = 9 Hz, 1H, H_A), 5.25 (sharp s, 1H, OH, exchanges slowly with deuterium oxide), 7.2-8.0 (m, 3H, H-3, H-4, and H-5 of pyridine), 8.7 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine); ms (chemical ionization, ammonia): M + 1 (223). Repeated attempts to obtain satisfactory elemental analyses were unsuccessful due to the instability of **10l**.

Erythro-1-hydroxy-1-(2-pyridinyl)-2-(1-pyrrolidino)propane (**11l**).

Reductive deoxygenation of **11c** (0.23 g., 1.03 mmoles) in 25 ml. of absolute ethanol using 10% palladium-on-charcoal (60 mg.), completion of the reaction as described under Procedure D and purification of the product by elution from a neutral alumina oxide column (10 g.) using 30 ml. of ethyl acetate-methanol (9:1 v/v) afforded 0.132 g. **11l** (62.9%) which decomposes slowly on standing; ^{1}H nmr: δ 0.92 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.0 (m, 4H, pyrrolidino H-3, H-4), 2.9-3.5 (m, 5H, H_M, pyrrolidino H-2, H-5), 5.22 (d, J_{AM} = 3 Hz, 1H, H_A), 6.75 (broad s, 1H, OH, exchanges with deuterium oxide), 7.0-7.9 (m, 3H, H-3, H-4, H-5 of pyridine), 8.55 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6); ms (chemical ionization, ammonia): M + 1 (207). Repeated attempts to obtain satisfactory elemental analyses were unsuccessful due to the instability of **11l**.

Threo-1-hydroxy-1-(3-pyridinyl)-2-(1-piperidino)propane (**10m**).

Catalytic deoxygenation of **10d** (0.586 g., 2.48 mmoles) in 50 ml. of absolute ethanol using 0.15 g. of 10% palladium-on-charcoal, completion of the reaction as described under Procedure D, and purification of the product by elution from a neutral alumina oxide column (30 g.) using 100 ml. of ethyl acetate-methanol (9:1 v/v) gave 0.446 g. of **10m** (81.7%); ^{1}H nmr: δ 0.78 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.62 (m, 6H, piperidino H-3, H-4, H-5), 2.1-2.95 (m, 5H, H_M, piperidino H-2, H-6), 4.28 (d, J_{AM} = 9 Hz, 1H, H_A), 4.9 (sharp s, 1H, OH, exchanges slowly with deuterium oxide), 7.28 (d, $J_{4,5}$ = 8 Hz of d, $J_{5,6}$ = 5 Hz, 1H, H-5 of pyridine), 7.78 (d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 1.75 Hz of d, $J_{2,4}$ = 1.75 Hz, 1H, H-4 of pyridine), 8.58 (m, 2H, H-2, H-6 of pyridine).

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.86; H, 9.15; N, 12.72. Found: C, 70.94; H, 9.10; N, 12.58.

Threo-1-hydroxy-1-(3-pyridinyl)-2-(4-morpholino)propane (**10n**).

Catalytic hydrogenation of **10e** (0.40 g., 1.68 mmoles) in 35 ml. of absolute ethanol using 10% palladium-on-charcoal (100 mg.), completion of the reaction according to Procedure D, and purification of the product by elution from a neutral alumina oxide column (20 g.) using 125 ml. of ethyl acetate gave 0.377 g. of **10n** (81.4%); ^{1}H nmr: δ 0.86 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.3-3.1 (m, 5H, H_M morpholino H-3, H-5), 3.85 (m, 4H, morpholino H-2, H-6), 4.35 (d, J_{AM} = 9 Hz, 1H, H_A), 5.1 (broad s, 1H, OH, exchanges with deuterium oxide), 7.32 (d, $J_{4,5}$ = 8 Hz of d, $J_{5,6}$ = 5 Hz, 1H, H-5 of pyridine), 7.8 (d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 1.75 Hz of d, $J_{2,4}$ = 1.75 Hz, 1H, H-4 of pyridine), 8.63 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine), 8.7 (d, $J_{2,4}$ = 1.75 Hz, 1H, H-2 of pyridine).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.97; H, 8.22; N, 12.43.

Threo-1-hydroxy-1-(3-pyridinyl)-2-(1-pyrrolidino)propane (**10o**).

Reductive deoxygenation of **10f** (0.558 g., 2.5 mmoles) in 55 ml. of absolute ethanol using 10% palladium-on-charcoal (0.15 g.), completion of the reaction as described under Procedure D and purification of the product by elution from a silica gel column (20 g.) using 150 ml. of ether-methanol (7:3 v/v) afforded 0.413 g. of **10o** (79.8%); ^{1}H nmr: δ 0.78 (d,

J_{MX} = 6.5 Hz, 3H, Me), 1.82 (m, 4H, pyrrolidino H-3, H-4), 2.5-3.1 (m, 5H, H_M, pyrrolidino H-2, H-5), 4.3 (d, J_{AM} = 9 Hz, 1H, H_A), 4.85 (sharp s, 1H, OH, exchanges slowly with deuterium oxide), 7.3 (d, $J_{4,5}$ = 8 Hz of d, $J_{5,6}$ = 5 Hz, 1H, H-5 of pyridine), 7.8 (d, $J_{4,5}$ = 8 Hz of d, $J_{4,6}$ = 1.75 Hz of d, $J_{2,4}$ = 1.75 Hz, 1H, H-4 of pyridine), 8.6 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 1.75 Hz, 1H, H-6 of pyridine), 8.68 (d, $J_{2,4}$ = 1.75 Hz, 1H, H-2 of pyridine); high resolution ms: exact mass calcd. for $C_{12}H_{18}N_2O$: 206.1419; found: 206.1420.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.85; H, 8.80; N, 13.58. Found: C, 70.39; H, 8.94; N, 13.29.

Threo-1-hydroxy-1-(4-pyridinyl)-2-(1-piperidino)propane (**10p**).

Catalytic reduction of **10g** (0.55 g., 2.33 mmoles) in 50 ml. of absolute ethanol using 10% palladium-on-charcoal (0.15 g.), completion of the reaction as described under Procedure D, and pufification of the product by elution from a neutral alumina oxide column (30 g.) using 75 ml. of ethyl acetate-methanol (9:1 v/v) gave rise to 0.332 g. of **10p** (64.7%); ^{1}H nmr: δ 1.02 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.8 (m, 6H, piperidino H-3, H-4, H-5), 2.35-3.15 (m, 5H, H_M, piperidino H-2, H-6), 4.42 (d, J_{AM} = 9 Hz, 1H, H_A), 5.5 (broad s, 1H, OH, exchanges with deuterium oxide), 7.45 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-3, H-5 of pyridine), 8.72 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-2, H-6 of pyridine).

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.86; H, 9.16; N, 12.72. Found: C, 70.53; H, 9.06; N, 12.61.

Threo-1-hydroxy-1-(4-pyridinyl-2-(4-morpholino)propane (**10q**).

Reductive deoxygenation of **10h** (0.36 g., 1.5 mmoles) in 40 ml. of absolute ethanol using 10% palladium-on-charocal (100 mg.), completion of the reaction as described under Procedure D and purification of the product by elution from a neutral alumina oxide column (30 g.) using 100 ml. of ethyl acetate-methanol (9:1 v/v) gave 0.269 g. of **10q** (80.3%); ^{1}H nmr: δ 0.84 (d, J_{MX} = 6.5 Hz, 3H, Me), 2.15-3.0 (m, 5H, H_M, morpholino H-3, H-5), 3.72 (m, 4H, morpholino H-2, H-6), 4.25 (d, J_{AM} = 9 Hz, 1H, H_A), 5.95 (sharp s, 1H, OH, exchanges slowly with deuterium oxide), 7.3 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-3, H-5 of pyridine), 8.55 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-2, H-6 of pyridine); high resolution ms: exact mass calcd. for $C_{12}H_{18}N_2O_2$: 222.1368; found: 222.1319.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 65.52; H, 8.32; N, 12.76.

Threo-1-hydroxy-1-(4-pyridinyl)-2-(1-pyrrolidino)propane (**10r**).

Catalytic deoxygenation of **10i** (0.50 g., 2.25 mmoles) in 50 ml. of absolute ethanol using 10% palladium-on-charcoal, (0.15 g.), completion of the reaction as described under Procedure D and purification of the product by elution from a neutral alumina oxide column (5 g.) using 50 ml. of chloroform as eluant yielded **10r** (0.287 g., 61.8%); ^{1}H nmr: δ 0.85 (d, J_{MX} = 6.5 Hz, 3H, Me), 1.82 (m, 4H, pyrrolidino H-3, H-4), 2.45-3.15 (m, 5H, H_M, pyrrolidino H-2, H-5), 4.26 (d, J_{AM} = 9 Hz, 1H, H_A), 4.75 (broad s, 1H, OH, exchanges with deuterium oxide), 7.35 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-3, H-5 of pyridine), 8.68 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz, 2H, H-2, H-6 of pyridine).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.85; H, 8.80; N, 13.58. Found: C, 69.89; H, 8.92; N, 13.45.

Acknowledgment.

We are grateful to the Natural Sciences and Engineering Research Council of Canada (Grant A0531) for financial support of this work.

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